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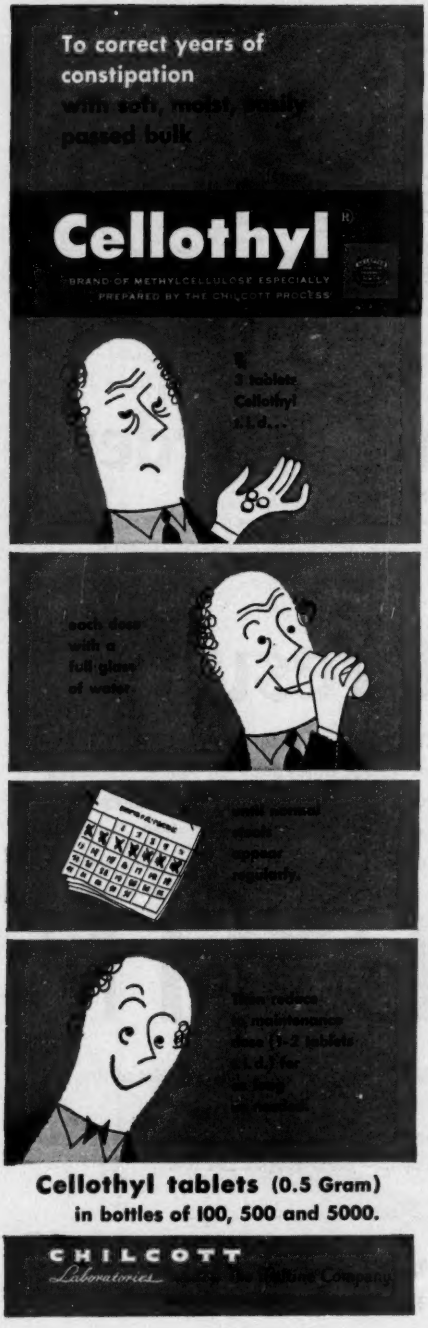
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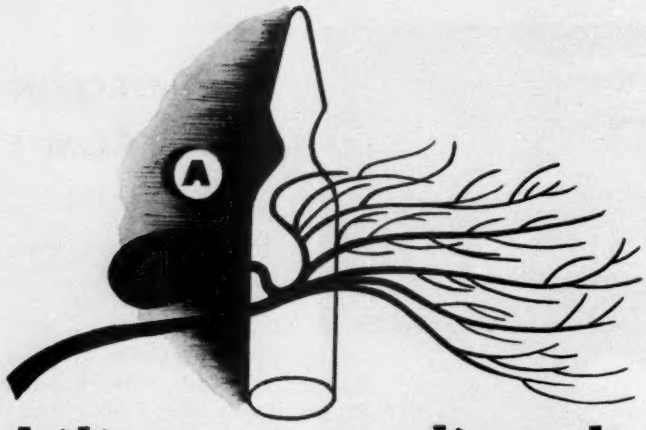
1. Newey, J. A., and Goetzl, F. R.: Permanente Med. Bull. 7:67 (July) 1949.



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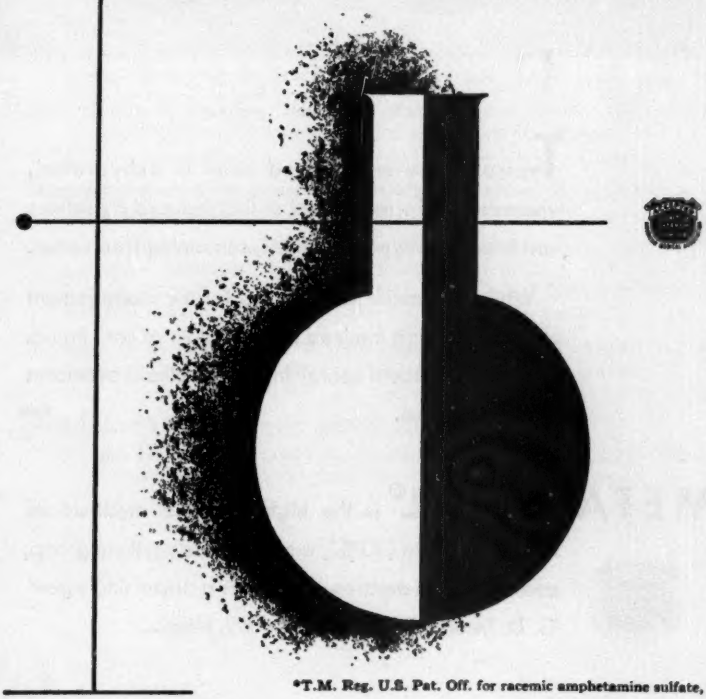

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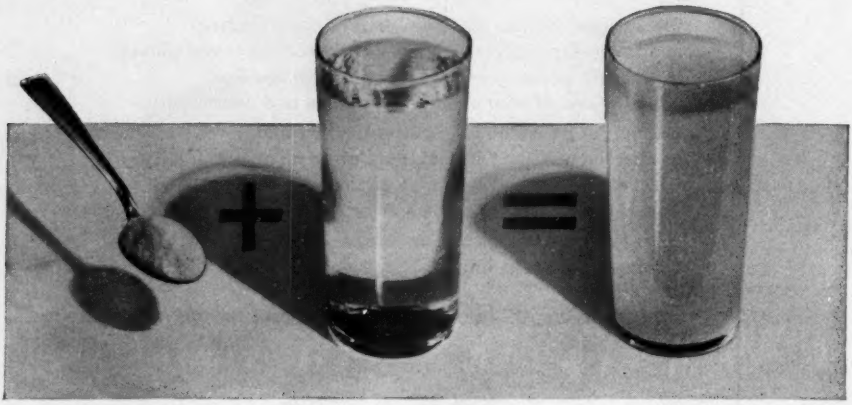

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ARCHIVES OF INTERNAL MEDICINE

VOLUME 88 JULY 1951 NUMBER 1

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A HORMONAL NEUROGENIC VASOPRESSOR MECHANISM

ROBERT D. TAYLOR, M.D.
IRVINE H. PAGE, M.D.
AND
A. C. CORCORAN, M.D.
CLEVELAND

CONCEPTS of the pathogenesis of essential hypertension have fluctuated widely during the half-century in which this disease has been recognized. One view is that hypertension is of diverse, probably multiple, causation, dependent on factors broadly classified as neurogenic, cardiovascular, endocrine and renal.[1] Among these, the participation of the nervous system was long ago considered especially significant, although no adequate explanation of the mechanism by which it might have this effect has been offered. Two observations in our experience pointed directly toward central nervous system participation in this disease. There were, first, the definition of the hypertensive diencephalic syndrome[2] and, second, the demonstration of a pressor substance in the cerebral ventricular fluid of patients with hypertensive disease.[3] Further, "neurogenic" hypertension has been defined as a common and early phase of essential hypertension.[4]

From the experimental aspect, Koch and Mies[5] described, and others have confirmed, the production of chronic neurogenic hypertension in dogs by buffer nerve section. Transitory and unstable hypertension has been produced in dogs by establishment of cerebral ischemia. A chronic, relatively stable form of neurogenic hypertension was elicited by adding to the effects of cerebral ischemia prolonged stimulation of the floor of the fourth ventricle.[6] Recent studies[7] supplement this

From the Research Division and the Frank E. Bunts Educational Institute, Cleveland Clinic Foundation.

1. Page, I. H.: The Nature of Hypertension, Bull. New York Acad. Med. **13**:645, 1937.

2. Page, I. H.: A Syndrome Simulating Diencephalic Stimulation Occurring in Patients with Essential Hypertension, Am. J. M. Sc. **190**:9, 1935.

3. Page, I. H.: A Highly Active Pressor Substance from Cerebral Ventricular Fluid of Human Beings, Science **82**:550, 1935; Physiological Properties of a Central Excitatory Agent in Fluid Obtained by Occipital Puncture of Man and Animals, Am. J. Physiol. **120**:392, 1937.

4. Page, I. H.; Taylor, R. D.; Corcoran, A. C., and Mueller, L.: Correlation of Clinical Types with Renal Function in Arterial Hypertension: II. Effect of Spinal Anesthesia, J. A. M. A. **124**:736 (March 11) 1944.

5. Koch, E., and Mies, H.: Chronischer arterieller Hochdruck durch experimentelle Dauerauschaltung von pressorreceptorischen Kreislaufnerven, Krankheitsforschung **7**:241, 1929.

6. Taylor, R. D.: The Use of Electromagnetic Induction for the Stimulation of Nervous Tissue in Intact Animals, Arch. Phys. Med. **28**:626, 1947.

7. Taylor, R. D., and Page, I. H.: Production of Prolonged Arterial Hypertension in Dogs by Chronic Stimulation of the Nervous System: Exploration of the Mechanisms of Hypertension Accompanying Increased Intracranial Pressure, Circulation **3**:551, 1951.

observation and demonstrate the existence of cerebral baroreceptors which alter arterial pressure in response to changes in intracranial spinal fluid pressure. Still other experiments [8] demonstrate in the cerebral vessels chemoreceptors which respond homeostatically to a variety of vasoactive drugs.

The course of some of the latter experiments directed attention to the existence of still another central nervous mechanism which acts on arterial pressure. In view

TABLE 1.—*Effects on Blood Pressure of Sensitized Dog B of Vasopressor Substance in Effluent Blood from Isolated Central Nervous System (Dog A) Elicited by Centripetal Vagal Stimulation* *

	Before Piperoxan Hydrochloride (20 Mg.) to Dog B						After Piperoxan Hydrochloride					
	Change of Blood Pressure During Vagal Stimulation of Dog A, Mm. Hg		Change of Blood Pressure After 0.01 Mg. of Epinephrine, Mm. Hg		Change of Blood Pressure After 0.01 Mg. of Arterenol, Mm. Hg		Change of Blood Pressure After Vagal Stimulation of Dog A, Mm. Hg		Change of Blood Pressure After Epinephrine 0.01 Mg., Mm. Hg		Change of Blood Pressure After Arterenol, 0.01 Mg., Mm. Hg	
Exp. No.	Control	Change	Control	Change	Control	Change	Control	Change	Control	Change	Control	Change
1	126	18	134	94	128	106	110	14	112	—48	114	6—8
2	106	22	110	40	106	44	106	24	106	—40	100	—6
3	100	18	104	50	100	60	84	16	88	—30	88	6
4	94	10	110	114	114	126			Dog died			
5	80	36	82	38	74	44	82	32	86	—24	84	8

* All blood pressure recordings are from dog B.

TABLE 2.—*Influence on Pressor Effects of Cerebral Vasopressor Substance Released in the Cord-Pithed Dog by Centripetal Vagal Stimulation of C-5968, TEAC, Piperoxan Hydrochloride and Priscoline®*

Exp. No.	Control Blood Pressure, Mm. Hg	Control Pressor Response, Mm. Hg	Response After Adequate TEAC (40-50 Mg./Kg.) to Augment Epinephrine and Arterenol Maximally, Mm. Hg		Response to Piperoxan Given Intravenously (20 Mg.) During Pressure Rise, Mm. Hg		Response After Adequate Piperoxan and Priscoline® to Cause Depressor Reaction from Intravenous Epinephrine and Arterenol, Mm. Hg		Response After C-5968 3 Mg./Kg., Mm. Hg		Effects of Renin Given at End of Experiment, Mm. Hg	
			Control	Change	Control	Change	Control	Change	Control	Change	Control	Change
1	130	42	80	120	102	28	120	110	106	—10	124	62
2	86	24	86	40	102	20	106	40	80	—10	76	74
3	72	16	72	30	...	..	76	28	76	— 6	...	..
4	112	28	82	34	134	24	100	24	84	4	86	62
5	130	20	126	32	...	..	118	30	120	— 8	...	..

of the novelty of the concept and its therapeutic implications, we submit for consideration this preliminary report.

METHODS AND RESULTS

1. *Cerebral Perfusion.*—The circulation of the central nervous system cephalad to C 5 of a dog (dog A) was isolated from the circulation of the rest of the body and perfused by a donor dog in a manner described elsewhere.[8a] The effluent jugular blood of the head of dog A

8. (*a*) Taylor, R. D., and Page, I. H.: Peripheral Vasomotor Effects of Adrenaline and Nor-Adrenaline Acting upon the Isolation Perfused Central Nervous System, Circulation, to be published; (*b*) Further Studies of the Cerebral Chemoreceptor Buffers as Influenced by Vasoconstriction and Vasodilator Drugs and Veratrum Viride, ibid, to be published.

was returned by an anastomosis to the jugular vein of dog B. Heparin was used as the anticoagulant and pentobarbital as the anesthetic. Both vagi of dog A were cut in the neck, but the cord and sympathetic chains were intact. Arterial pressures were recorded by mercury manometers from the cannulated femoral arteries. In these five experiments, dog B was sensitized to the actions of vasopressor substances by bilateral nephrectomy and administration of tetraethylammonium chloride (TEAC).[9] Pressor responsiveness of dog B was tested by intravenous injections of 0.01 mg. of epinephrine and arterenol (nor-epinephrine).[10]

The central end of one or other or both vagi of dog A (the isolated head) were stimulated with a sinusoidal current of an intensity of about 50 milliamperes. Stimulation carried on for two to six minutes resulted in a slow rise of arterial pressure in dog B which slowly dis-

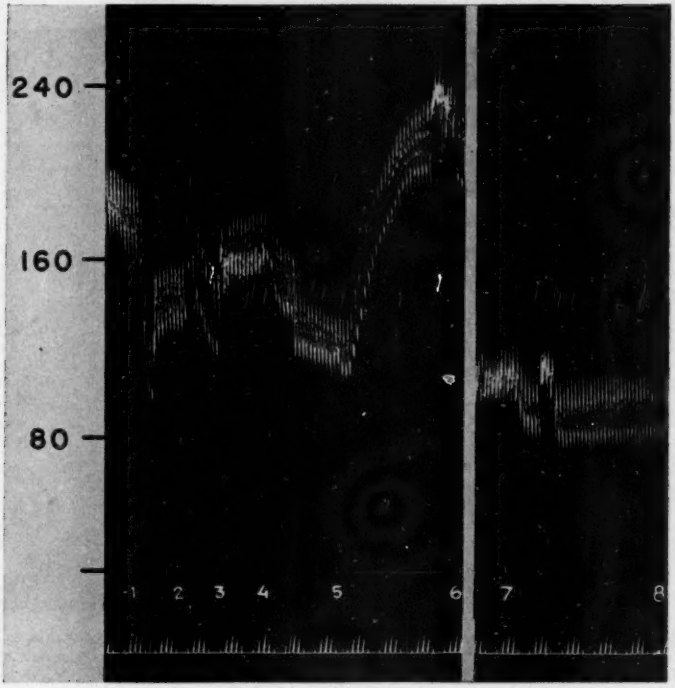

Fig. 1.—Blood pressure response of cord-pithed dog (experiment 1) to centripetal vagal stimulation as influenced by piperoxan hydrochloride, priscoline® and C-5968: *1*, epinephrine, 0.01 mg. intravenously, after 20 mg. of piperoxan hydrochloride; *2*, arterenol, 0.01 mg. intravenously, after 20 mg. of piperoxan hydrochloride; *3*, priscoline,® 3 mg. per kilogram of body weight; *4*, arterenol, 0.01 mg. intravenously; *5*, centripetal stimulation of vagi, 50 milliamperes; *6*, stimulus discontinued (C-5968 was injected in three successive doses of 1 mg. per kilogram, with gradual diminution of pressor response to vagal stimulation [not shown]); *7*, centripetal stimulation of vagi; *8*, stimulus discontinued.

9. Page, I. H., and Taylor, R. D.: Augmentation of Vasoactive Substances by Tetraethyl Ammonium Chloride, Circulation **1**:1233, 1950.

10. Supplies of these substances were made available by Mr. W. A. Curran, Winthrop-Stearns, Inc., New York.

appeared after the stimulation was stopped (table 1). Piperoxan (benodaine®; benzodioxane) hydrochloride (20 mg.) was given intravenously to dog B. The test dose of epinephrine was then depressor and the action of arterenol greatly inhibited. Stimulation of the vagi of dog A again resulted in increased arterial pressure in dog B.

2. *Cord Pithing.*—Destruction of the spinal cord distal to the sixth cervical segment was effected in 5 dogs by laminectomy and pithing one or two days before the experiment. On the day of the experiment, the dogs were anesthetized with pentobarbital, the femoral artery cannulated for pressure recording, the femoral vein cannulated for injection and the vagi exposed in the neck and cut as before. When necessary, respiration was supported by a respirator and intratracheal catheter. Test doses of epinephrine and arterenol were given, after which the vagi were stimulated in the manner noted above. As in the preceding experiment, stimulation

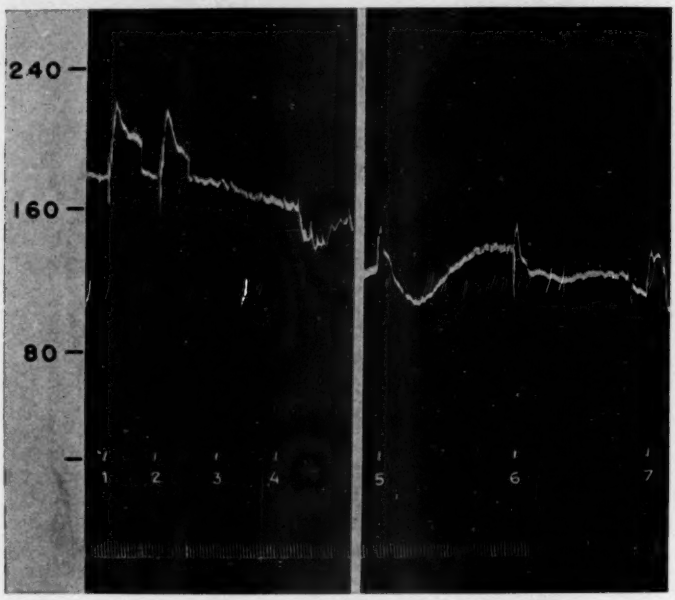

Fig. 2.—Effects of intravenous injection of C-5968 on pressor responses of a dog to intravenous injection of serotonin. *1* and *2*, serotonin; *3* and *4*, C-5968, 1 mg. per kilogram of body weight; *5* and *6*, serotonin; *7*, angiotonin.

caused a gradual rise of arterial pressure, which sometimes persisted for 5 to ten minutes after stimulation was stopped (table 2). TEAC was then given in repeated doses of 5 mg. per kilogram each at such intervals as were required to elicit maximum augmentation of the pressor actions of epinephrine and arterenol. The dosage totaled up to 40 to 50 mg. per kilogram of body weight and had the effect of greatly augmenting the pressor responses obtained on centripetal vagus stimulation. Piperoxan hydrochloride was given to reverse the action of epinephrine and depress that of arterenol. Priscoline® (2-benzylimidazoline hydrochloride) (2 to 4 mg. per kilogram) was given intravenously with the result that both epinephrine and arterenol responses became depressor. Stimulation of the vagus at this time resulted in pressor effects as great as had been observed before administration of sympatholytic drugs. Administration of piperoxan hydrochloride during the periods of vagus stimulation resulted in augmentation of the pressor response.

C-5968 (*l*-hydrazinophthalazine)[11] in three successive intravenous doses of 1 mg. per kilogram each was found to abolish the pressor effect of centripetal vagus stimulation. This effect had been progressively inhibited by the first and second doses. The dogs remained fully responsive to test doses of renin. Significant graphs of a representative experiment are shown in figure 1. In two other experiments, dogs similarly prepared were treated with C-5968 early in the experiment, before administration of piperoxan and priscoline.® C-5968 was again found to block the pressor effect of centripetal vagus stimulation. Pressor effects of epinephrine and arterenol were slightly depressed by C-5968 but could still be potentiated by administration of tetraethylammonium chloride and later blocked by the sympatholytics.

3. *Serotonin and C-5968.*—In experiments on vascular reactivity similar to those previously described, pressor responses were determined for epinephrine, arterenol, angiotonin, renin and serotonin.[12] In two experiments in dogs anesthetized with pentobarbital, administration of C-5968 in two doses of 1 mg. per kilogram each was found to alter the response to serotonin. Whereas it had been a pure pressor, the response became biphasic, with an initial slight rise, followed by a sustained fall. Pressor effects of other agents were slightly impaired, as were also the depressor effects of acetylbetamethylcholine (mecholyl®) chloride and nitroprusside (table 3).

TABLE 3.—*Effect of l-Hydrazinophthalazine on Vascular Reactivity in Normal Dog Under Pentobarbital Anesthesia*

Drug	Control Blood Pressure, Mm. Hg	Change in Blood Pressure, Mm. Hg	Time
Arterenol	168	92	1:51
Acetylbetamethylcholine chloride	172	−78	1:59
Nitroprusside	178	−90	2:08
Serotonin	162	46	2:07
Serotonin	162	38	2:10
C-5968 1 mg./Kg.	162	−14	2:15
C-5968 1 mg./Kg.	148	−22	2:18
Arterenol	140	74	2:31
Serotonin	110	+22 −18	2:35
Serotonin	122	+12 −18	2:42
Angiotonin	94	26	2:48
Acetylbetamethylcholine chloride	110	−40	2:58
Nitroprusside	96	−46	3:00
Renin	84	86	3:07

COMMENT

Claude Bernard held the view that every organ is in some respect endocrine. The experiments reported above show that this is true of the brain. Nerve tissues are known to form three pressor substances: epinephrine, arterenol and pitressin. Our experiments demonstrate that still another pressor substance can be made to appear in jugular blood. We provisionally believe it to be of nerve origin.

This substance is pharmacologically distinct from epinephrine and arterenol and from renin and angiotonin. It is differentiated from pitressin by its lack of tachyphylactic effect and, in our hands, by a lack of inhibition of pitressin by C-5968. Like serotonin, it is greatly inhibited by C-5968. Serotonin[13] is the naturally

11. Furnished by Dr. F. F. Yonkman, Ciba Pharmaceutical Products, Inc., Summit, N. J.

12. Page, I. H., and Taylor, R. D.: Variations of Vascular Reactivity in Normal and Hypertensive Dogs, Am. J. Physiol. **156**:412, 1949.

13. Rapport, M. M.; Green, A. A., and Page, I. H.: Crystalline Serotonin, Science **108**:329, 1948.

occurring pressor and vasoconstrictor substance formed during the clotting of blood. Chemically its active group is similar to or identical with dihydroxytryptamine.[14] Our evidence demonstrates a common property of serotonin and the vasopressor substance of cerebral origin. It may be that serotonin is the type substance of a new and important series of pressor compounds, of which the cerebral pressor substance is one.

While the cross circulation experiments were in progress, our attention was drawn by Dr. Jiminez Diaz to a study of the mechanism of arterial pressure regulation.[15] Skilful cross transfusion experiments demonstrated that stimulation of the central end of the vagus elicits liberation into the blood of a pressor substance. This they believed to arise from arterial walls. Its precursor is termed "arterin" and the effector substance "arteriohypertensin." It seems probable that the vasopressor substance of cerebral origin which we postulate was concerned in these responses. But epinephrine, arterenol, renin and its effector, angiotonin, may also participate in the vigorous reaction which follows such electrical stimulation in animals with intact nervous systems. Similarly, we ascertained that Binet and Burstein [16] had demonstrated liberation of a vasoconstrictor as the result of centripetal vagus stimulation. It differed from epinephrine in that its action was not blocked by administration of piperoxan. They [17] considered it to be posthypophysial in origin and assumed it to be pitressin. Pressor effects from centripetal stimulation of the vagus had been previously reported by Chang and Lim [18] and by Sattler.[19]

If it should be established that such a mechanism operates in chronic hypertensive disease, most of the inconsistencies of our present knowledge of these conditions would be resolved. On theoretical grounds, it seems likely that the vasopressor substance of cerebral origin is an amine, as are most pressor substances. Olsen [20] seems to have demonstrated a considerable inhibition of renal tryptamine oxidase in ischemic kidneys of hypertensive rats. The possibility arises that a serotonin-like pressor system is concerned secondarily in the mechanisms of renal hypertension.

Participation in essential hypertension of a pressor substance of cerebral origin, unaffected by agents which wholly block adequate doses of epinephrine and arterenol, would resolve some of the paradoxes of our knowledge of the altered physiology of this disease. For example, piperoxan hydrochloride characteristically causes a

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14. Rapport, M. M.: Serum Vasoconstrictor (Serotonin): IV. Presence of Creatinine in the Complex; Proposed Structure of the Vasoconstrictor Principle, J. Biol. Chem. **180**:961, 1949.

15. Diaz, C. J.; de la Barreda, P.; Candeira, J. S., and Alcala, R.: Additional Studies on the Function of the Vascular Wall in Arterial Pressure Regulation, Bull. Inst. M. Res., Univ. Madrid **3**:131, 1950.

16. Binet, L., and Burstein, M.: Sur le pouvoir vasconstricteur du sang artériel après excitation centripète du nerf vague chez le chien, Compt. rend. Soc. biol. **143**:1344, 1949.

17. Binet, L., and Burstein, M.: Passage dans le sang d'une substance vasoconstrictrice d'origine céphalique après excitation centripète d'un nerf vague chez le chien, Compt. rend. Soc. biol. **143**:1347, 1949.

18. Chang, H. C., and others: Vagus-Post-Pituitary Reflex: Oxytocic Component, Chinese J. Physiol. **12**:309, 1937; **13**:269, 1938.

19. Sattler, D. G.: Vago-Neurohypophsial Pressor Reflex, Proc. Soc. Exper. Biol. & Med. **44**:82, 1940.

20. Olsen, N. S.: Oxidations Mediated by Normotensive and Hypertensive Tissues, Federation Proc. **10**:99, 1951.

pressor response in essential hypertension; similarly, it augments the pressor effect of centripetal vagus stimulation in cord-pithed dogs. The view has been widely held that essential hypertension is the result of disordered activity of vasomotor nerves. Sympathectomies are performed on this physiologically scant basis. Results of these operations are very often disappointing. Indeed, it has been observed [21] that patients with "neurogenic" hypertension and with the hypertensive diencephalic syndrome are rarely benefited by extensive lumbodorsal sympathectomy, whereas, were their disease dependent only on vasomotor mechanisms, the results should be very good. This paradox can be resolved if, as now seems likely, their hypertension is neurogenic enough but humorally as well as neurally mediated. The frequently used comparison of acute anxiety with early essential or "neurogenic" hypertension is unsatisfactory. In anxiety, the blood pressure may rise but renal blood flow falls. In early hypertension, the blood pressure is high but renal blood flow is often normal,[22] while efforts to uncover latent anxiety have been unconvincing.

Reubi [23] was the first to demonstrate the hypotensive and renal vasodilator properties of C-5968 in patients with essential hypertension. This observation has been confirmed elsewhere.[24] Page and McCubbin [25] have demonstrated that it causes profound and prolonged lowering of arterial pressure in both chronic neurogenic (buffer nerve section) and renal hypertensive (perinephritis) dogs. Clinically, over a brief period, we have found it effective in widely differing forms of hypertensive disease. In patients, as in dogs, its effectiveness is not confined to "neurogenic" hypertension.

The fact that *l*-hydrazinophthalazine is active in etiologically distinct types of hypertension and that it acts by inhibiting a cerebral vasopressor substance suggests that the latter substance may participate in varying degree in more than one form of hypertensive disease.

SUMMARY AND CONCLUSIONS

Cross circulation experiments and observations in dogs with spinal cords pithed below the sixth cervical segment and both vagi cut in the neck confirm the liberation into the blood of a vasopressor substance on centripetal vagus stimulation.

This substance is shown to be distinct from epinephrine, arterenol (nor-epinephrine), renin, angiotonin and pitressin.

Its activity is enhanced by large doses of tetraethylammonium chloride and inhibited and ultimately abolished by *l*-hydrazinophthalazine (C-5968). This drug also inhibits the pressor action of serotonin.

On appropriate stimulation, the brain can act as an endocrine organ, which releases a pressor substance into the blood.

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21. Taylor, R. D.; Corcoran, A. C., and Page, I. H.: Unpublished observations. de Takats, G.; Graupner, G. W.; Fowler, E. F., and Jensik, R. J.: Surgical Approach to Hypertension: Second Report, Arch. Surg. **53**:111 (Aug.) 1946.

22. Corcoran, A. C.; Taylor, R. D., and Page, I. H.: Functional Patterns in Renal Disease, Ann. Int. Med. **28**:560, 1948.

23. Reubi, F.: Influence of Some Peripheral Vasodilators on Renal Circulation, Helvet. med. acta **16**:297, 1949.

24. Schroeder, H.: Personal communication to the authors, 1951.

25. Page, I. H., and McCubbin, J.: Unpublished observations, 1951.

The therapeutic properties of a phthalazine derivative (C-5968) in human beings and in dogs with hypertension of varied origins are consistent with this hypothesis.

ADDENDUM

Since this manuscript was submitted, experiments on anesthetized dogs in which sympatholysis had been effected by piperoxan, priscoline® and TEAC demonstrate that release of the cerebral vasopressor substance follows centripetal stimulation of the cut sciatic nerve. It seems likely that activation of this mechanism is a response common to many forms of neural stimulation.

CATION EXCHANGE RESIN IN TREATMENT OF THE NEPHROTIC SYNDROME

RICHARD W. LIPPMAN, M.D.
LOS ANGELES

THE USE of cation exchange resin for the relief of edema was first suggested by Dock [1] in 1946. Since that time, several studies have been performed on animals [2] and on man [3] with results that were summarized by Dock [4] in 1950. These experiences have indicated that treatment with the cation exchange resin is of real value in the control of cardiac edema and edema from other sources. However, difficulty has arisen from several sources during the administration of resin.

This paper deals with the observation of effects and toxicity of cation exchange resin in 14 patients with the nephrotic syndrome, treated during a period of one year. It is a compilation of several experiences which have demonstrated the striking benefits that may accrue to the nephrotic patient from resin administration and also the danger of the severe toxicity that may occur.

METHODS AND MATERIALS

The cases of nephrotic syndrome in the 14 patients studied were well documented. All were considered to have the degenerative stage of glomerular nephritis, except two patients who were diabetic, with Kimmelstiel-Wilson syndrome.

Of these patients nine were male and five female. The youngest was 11 months and the oldest 74 years of age. The duration of their illness before treatment ranged from two weeks to 28 years. All but two of the patients had evidence of impaired renal function, according to the endogenous creatinine clearance. Of these, only two were frankly uremic, with gross elevation of the serum creatinine concentration.

The cation exchange resin used was WIN 3000,[5] a resin which releases ammonium ions in exchange for other cations. The material was administered, in all but one case, in the form of

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From the Institute for Medical Research, Cedars of Lebanon Hospital.

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1. Dock, W.: Tr. A. Am. Physicians **59**:282, 1946.

2. (*a*) Crismon, J. M.: Abstracted, Federation Proc. **8**:30, 1949. (*b*) Ch'en, J. S., and Freeman, S.: J. Lab. & Clin. Med. **35**:99, 1950. (*c*) McChesney, E. W., and McAuliff, J. P.: Am. J. Physiol. **160**:264, 1950. (*d*) Danowski, T. S.; Greenman, L.; Mateer, F.; Peters, J. H.; Weigand, F. A.; Mermelstein, H., and Clarke, C. E.: Abstracted, J. Clin. Invest. **29**:807, 1950.

3. Danowski and others.[2d] Irwin, L.; Berger, E. Y.; Rosenberg, B., and Jackenthal, R.: J. Clin. Invest. **28**:1403, 1949. Kahn, S. S., and Emerson, K., Jr.: Abstracted, ibid. **29**:827, 1950. Currens, J. H.; Counihan, T., and Rourke, M.: Abstracted, ibid. **29**:807, 1950. Kraus, H.: Abstracted, ibid. **29**:829, 1950.

4. Dock, W., and Frank, N. R.: Am. Heart J. **40**:638, 1950.

5. WIN 3000 was provided generously by the Research Department, Winthrop-Stearns, Inc., New York 13.

golden brown 20 to 40 mesh size granules. The granules are tasteless and odorless, completely insoluble in water and cannot be suspended well, since they settle immediately after mixing.

The patients were under observation for varying times before the administration of resin. During the control periods, they all had constant or increasing weight, massive anasarca and ascites. Many determinations were made of the Addis count, quantitative protein excretion, chloride excretion, endogenous creatinine clearance, serum sodium and potassium and, in most cases, the carbon dioxide-combining power. Other usual diagnostic data were also obtained before the start of the resin treatment.

During the first period, resin administration was done in the hospital. All voided urine was obtained, with few exceptions, for each patient during the crucial days of observation. Total fluid consumption was measured, and the morning body weight was obtained daily. All the determinations mentioned were repeated at least once during the height of diuresis and at intervals thereafter.

RESULTS

An excellent diuresis was obtained in 11 of the 14 patients. Most of the patients who responded to resin administration have been maintained virtually free of edema for periods that vary up to one year. For several patients the difference in their clinical condition since the initiation of resin therapy can be compared to the dramatic effects produced by cortisone administration in a patient with severe rheumatoid arthritis. For example, one patient, who was bedridden for 18 months with profound anasarca, after a complete diuresis has returned to his former occupation with no disability, although he continues to show the blood and urinary changes characteristic of continuing glomerular nephritis (case 1).

Of the three patients who did not have diuresis, two were unable to take the resin in adequate amounts. Of the latter, one was a child. The other was uremic, with nausea and vomiting. The remaining patient apparently took adequate doses of the resin for a sufficient time, but no diuresis occurred.

No specific effect on the renal lesion has been noted in any patient.

DOSE AND ADMINISTRATION

To adults the resin was administered with a spoon, followed by a drink of water. There was little objection to the tasteless and odorless resin, although some objected mildly to the gritty consistency. It was found that a level measuring teaspoonful weighed 4 Gm. The initial adult dose was 8 Gm. four times a day before each meal and at bedtime. In all patients who responded with a diuresis to the treatment, a dose of 12 Gm. four times a day (48 Gm. per day) or less was sufficient. If there was no loss of weight and no increase in the urinary volume after 48 hours, each individual dose was increased by 4 Gm. increments every 48 hours, until a result was obtained or until the individual dose reached 24 Gm., when the administration was abandoned. The dose for children was larger than would be anticipated from the difference in body size. In those children who responded, with a "dry body weight" of 30 to 50 pounds (13.6 to 22.7 Kg.), the effective dose was 8 Gm. four times a day.

Administration to children was difficult, since the resin, though not very objectionable, became tiresome to take and difficult to disguise. It was imperative to separate the child from the home during the initiation of treatment. Impersonal,

calm insistence by the nurse was of paramount importance in establishing an initial favorable and cooperative response by the child.[6] After the pattern was established, the mother came and observed the nurse's technique and, finally, tried it herself before the child was discharged.

For children the resin can be partially camouflaged with puréed fruit, jelly or syrup. It can be baked into breads and cake or incorporated into candies without impairing its effectiveness, but this bothersome procedure has not helped appreciably in the administration. The resin can be pulverized into a fine, tan powder. This powder can be more easily incorporated into syrupy mediums and lacks the objectionable grittiness. In addition, by increase of the adsorption surface that results from smaller particle size, the powder is considerably more effective, so that a smaller dose must be used. The powder was given to only one patient (case 2), with near disastrous results, since the increased potency of the powdered resin was not fully appreciated. It would seem that the powder is required in one-fourth the dose recommended above, or less. However, the powder is difficult to prepare because of the resin's hardness, and its preparation in quantity requires more strenuous methods than are available in the average pharmacy. As a rule, the resin is administered for five days, with a two day interval, followed by another course of administration, until the edema is nearly completely gone. Two or three such courses usually suffice, and the lapse in treatment prevents the occurrence of acidosis and electrolyte deficiencies, which will be discussed further on. When the "dry body weight" is approached, treatment is stopped. The weight and presence of edema are followed daily until 2 or 3 pounds (0.9 or 1.3 Kg.) has been gained. At this point, a two or three day course of resin administration is usually sufficient to restore the optimum body weight. In growing children and emaciated adults it is necessary to distinguish between the reaccumulation of edema fluid and growth with an increase in body weight. In successful cases, the necessity for resin administration usually diminishes as time passes, the intervals between treatment increase and some patients have become edema free as the result of a remission.

TOXIC EFFECTS

Acidosis.—Strongly basic ions, most notably sodium and potassium, are adsorbed by the resin in the intestinal tract. In this way the body's store of available base is depleted. In addition, the resin liberates ammonium in exchange. This is a weakly basic ion and is absorbed together with strong acidic ions, such as chloride. The result is an effect similar to that from the administration of ammonium chloride. If the kidney is competent, the danger is not so great as otherwise, since the normal renal acid-base regulatory mechanism is able to meet the increased functional load. The urine becomes strongly acid, with a pH as low as 5.0, or even lower, and the chloride excretion rate is concomitantly increased.

However, in the patient with some diminution of renal function, severe acidosis can occur with great rapidity. It is necessary to know the carbon dioxide-combining power of the blood at frequent intervals, and, when the value falls below 30 volumes per cent, the resin administration is immediately discontinued. Usually a 48 hour hiatus in the treatment, with fluid consumption encouraged, is sufficient to correct

6. The Pediatric Nursing Staff, Cedars of Lebanon Hospital, cooperated completely in this study, especially in skilful administration of the resin and collection of urine from young children.

the acidosis. During this time, the diuresis usually slows but is not abolished. Occasionally, it may become necessary to administer sodium or potassium bicarbonate by intravenous infusion if the acidosis is permitted to progress to a dangerous level. If such alkalis are given intravenously, care must be used, since the patients may easily be pushed over into alkalosis.

Particular care, with respect to the occurrence of acidosis, must be taken with patients in frank renal failure, since their renal acid-base regulatory mechanism is severely impaired and will fail under a much smaller load than the normal mechanism can tolerate. In addition, diabetic subjects are prone to the easy development of acidosis and may rapidly enter combined renal and diabetic acidosis. In children, since they often cannot complain of symptoms that may warn the physician, special attention must be given to their general behavior and alertness (case 3). At the first sign of apathy, weakness or drowsiness, treatment with the resin should be discontinued.

Hypokalemia and Hyponatremia.—The cation exchange resin does not specifically adsorb sodium ion. Ammonium is released in exchange for any cation in the environment. Since sodium is preponderant in the body fluids, more of this ion is removed. However, potassium is also removed in large amounts. The resin adsorbs not only the cations in the foods and fluids consumed but also those that are secreted in the gastrointestinal juices. In this way a severe deficiency in potassium may be produced (case 4).

Although hypokalemia is more likely to occur as the "dry body weight" is approached, it may also occur in the face of severe edema. When hypokalemia is detected by the symptoms of weakness and confusion, by the electrocardiographic changes and by serum potassium determination, potassium chloride should be administered by mouth or, in severe deficiencies, intravenously. Large quantities of potassium may be required to restore the serum concentrations to a normal level. It may be supposed that the musculature is depleted of its potassium to maintain the normal serum level and that when the latter falls it is necessary to replenish the muscles before restoration of the serum concentration is completed.

When the resin is administered continuously for a period longer than five days, it may be necessary to administer potassium chloride by mouth, simultaneously, to prevent excessive potassium depletion. In an adult 1 Gm. with each dose of resin usually suffices.

Patients with the nephrotic syndrome frequently have a low serum sodium concentration, and, therefore, it is necessary to know the pretreatment level for comparison. However, such an initial low serum sodium concentration does not contraindicate treatment, and the concentration may even rise during treatment, with the relief of edema. Aggravation of hyponatremia, with symptoms, does not occur until the edema fluid has been completely removed.

Deficiencies of Other Cations.—Since the resin can be expected to adsorb all cations in proportion to their respective concentrations in the gastrointestinal tract, deficiencies in other cations may be expected to occur with prolonged administration. Effects on metabolism of the trace elements are not known. The removal of calcium has not proved to be significant. When resin was administered for long periods, a month or more, microcytic, hypochromic anemia sometimes occurred, and this has been attributed to iron deficiency. The anemia can be corrected either by the

administration of iron or by withdrawal of the resin treatment. However, when the resin is administered intermittently for short periods, such deficiencies have not been encountered.

COMMENT

The use of cation exchange resins for the treatment of edema represents an ingenious application of principles previously used for industrial purposes, such as water softening. Exchange resins may be made with widely varying characteristics, and it is within the range of possibility to produce resins that are more effective for the treatment of edema, as well as other resins which may be used to eliminate substances that accumulate during the failure of excretory function. As an example, the adsorption of urea and creatinine has been demonstrated in vitro with cation exchange resins.[7] In all my patients a fall in the serum creatinine concentration has accompanied the administration of resin. However, a transient rise in the endogenous creatinine clearance accompanies diuresis, and the fall in serum creatinine concentration may not be related to adsorption by the resin of creatinine in the intestine.

One further application of the resin may be useful, even in its present form. Patients with uremia in whom there has been an accumulation of potassium, with symptoms from hyperkalemia, may be relieved by administration of the resin concomitantly with sodium salts by mouth. In this way the depletion of sodium can be avoided while potassium is removed.

The cation exchange resin can be prepared in various forms, so that other ions than ammonium are released in exchange for cations in the environment. It would seem reasonable to believe that a mixture of such resins could be prepared, balancing ammonium, potassium, calcium and iron forms of the resin,[8] so that such complications as acidosis and hypokalemia could be avoided in most instances.

Even in their present, incompletely developed form, the resins certainly have a useful application in control of the nephrotic state with edema.

REPORT OF CASES

CASE 1.—T. M. is a male writer, aged 41, who was reported to have had "Bright's disease" at the age of 13. At that time he was known to have proteinuria and was kept in bed for two months. Other details are lacking. At the age of 20 he first had the symptoms of duodenal ulcer and two years later had a massive hemorrhage from the ulcer, requiring hospitalization. At the age of 25, he was rejected for a life insurance policy but a year or two later passed the physical examination. In 1940, when he was 32 years of age, his blood pressure was observed to be 180 systolic, and the urine was noted to contain protein and red blood cells. From that time on his systolic tension was constantly elevated, and in 1946 he had some episodes of nocturnal dyspnea. From July 1948 to September 1949 there were generalized anasarca and ascites, with complete disability, in spite of a salt-free diet.

When he was seen in September 1949, there was evidence of cardiac decompensation, with pulmonary rales, tachycardia and enlargement of the liver. Massive proteinuria was present, with epithelial cells, many red blood cells and casts. Blood casts were seen on several examinations, and the urine remained substantially unchanged throughout the subsequent course, although the cardiac decompensation was relieved with relative ease during resin administration. The fol-

7. Gerhke, C. W., and Almy, E. F.: Science **110**:556, 1949.

8. The resins which have been released to the market since this paper was prepared do not meet this suggestion. Death due to hypokalemia and acidosis has been observed in one patient treated elsewhere with a commerical resin that was partially saturated with potassium.

lowing serum determinations were made: sodium 325 mg., calcium 12.6 mg., creatinine 2.4 mg., nonprotein nitrogen 61 mg. and cholesterol (total) 173 mg., per 100 cc. His blood pressure at this time was 230/120.

He was considered to have glomerular nephritis with the nephrotic syndrome, azotemia and secondary hypertension with heart failure. At this point treatment was instituted with the cation exchange resin. His course is illustrated in figure 1. There was a remarkable change in his clinical condition. His weight diminished from a maximum of 176 pounds (79.8 Kg.) to a minimum of 133 pounds (60.3 Kg.). At the end of the diuresis period he experienced some nausea and weakness. At this time the serum potassium concentration was 11.7 mg. per 100 cc. Potassium iodide was given by mouth for three days, with relief of the nausea. It was necessary to administer resin again in November and twice in January 1950 for short periods, but not since then. He has been entirely free of edema and has gained weight as a result of improved nutrition. At present he looks fine and is working at his usual occupation as a writer. The urinary findings are exactly the same as they were before treatment. The serum creatinine concentration, which fell during treatment, has gradually risen to its present level, in the neighborhood of 2.5 mg. per 100 cc.

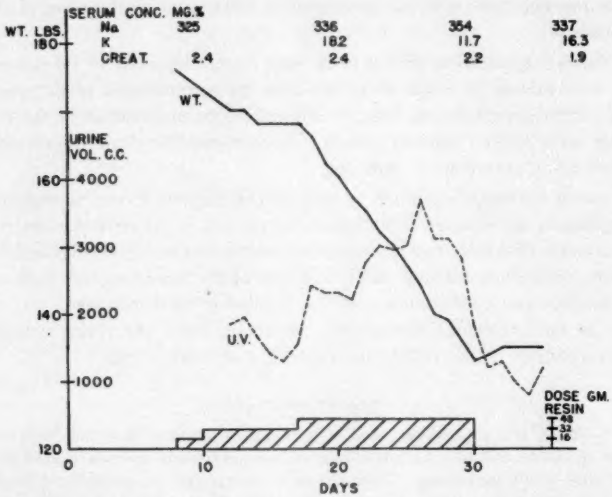

Fig. 1 (case 1).—Response to resin administration, illustrating fall in serum potassium and creatinine concentrations.

Case 2.—Patient G. D. is a boy, aged 4, who in May 1949 had an infection of the upper respiratory tract, with fever and sore throat. He recovered in 24 hours, but in mid-June his eyelids appeared to be slightly puffy and the urine contained protein. At first only a few granular casts were seen, and there was no blood in the urine. But by mid-July the urine contained large amounts of protein, casts and some red blood cells. When seen in August 1949, he was observed to have moderate periorbital edema, slight pretibial edema and a protuberant abdomen with ascites. Results of physical examination were otherwise normal. At that time the urine contained large amounts of protein, many white and epithelial cells, red blood cells and casts. Blood casts and oval fat bodies were seen. The serum cholesterol concentration was 448 mg., the total serum protein concentration was 5.1 Gm. and the serum creatinine concentration was 1.1 mg. per 100 cc.

During September, his edema increased markedly and his weight increased from 44 to 50 pounds (20 to 22.7 Kg.). At that time treatment was started with the cation exchange resin, and he took it well. His weight dropped from 50 to 38 pounds (22.7 to 17.2 Kg.) in one week,

with complete relief from edema and ascites. However, he soon began to reaccumulate fluid, and by November his weight was again up to 50 pounds. During the interval the child had become recalcitrant about taking the resin, and, in order to make it more palatable, a portion of the resin was finely ground to a powder so that it could be incorporated into foods without recognition of the consistency. In spite of all these efforts, the child took resin irregularly. In addition, the same dose of resin was administered in the powdered form that had been used previously in the granular form. The difference in effectiveness that would be caused by smaller particle size was not appreciated, and there was reason to believe, from experiments performed in vitro, that the effectiveness might not be significantly altered.

On November 19 the child seemed a little drowsy in the afternoon, and by morning he was comatose with hyperventilation. At this time, the serum creatinine concentration was 1.7 mg., the serum sodium concentration 280 mg. and the serum potassium concentration 11.8 mg. per 100 cc. The carbon dioxide-combining power was 9.2 volumes per cent. The serum chloride concentration was 615 mg. per 100 cc. The systolic pressure was 120 and the diastolic pressure could not be obtained. During the next 24 hours the child received 2,500 cc. of sixth-molar sodium lactate intravenously, to which were added 3 Gm. of potassium chloride and 1,000 cc. of 5 per cent dextrose solution in 0.85 per cent sodium chloride solution. The serum creatinine concentration fell to 1.07 mg., the serum sodium concentration rose to 297 mg. and the serum

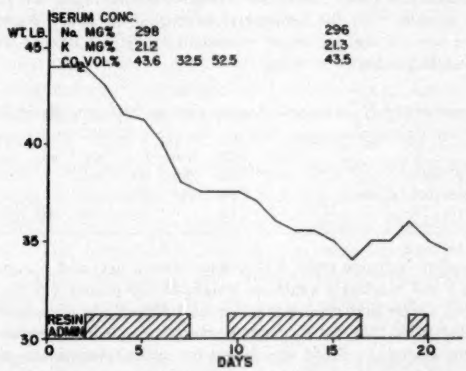

Fig. 2 (case 3).—Response to resin administration (32 Gm. daily), illustrating fall in carbon dioxide-combining power, with rapid return to normal on withdrawal of treatment with resin.

potassium concentration was 11.0 mg., per 100 cc. The carbon dioxide-combining power rose to 27 volumes per cent. During the succeeding 24 hours an additional liter of sixth-molar sodium lactate and 1 liter of 5 per cent dextrose solution in 0.85 per cent sodium chloride solution were given, with 6 Gm. of potassium chloride added. He became conscious and appeared normal. No change occurred in the degree of edema, and the carbon dioxide-combining power was now 45 volumes per cent. He did well after this, and no further resin was given.

CASE 3.—Patient M. A. was a boy, aged 3, who had been perfectly well until June 1950, when the parents noticed swelling of the abdomen. In July 1950 he also began to have periorbital edema, which was attributed to an allergy. On August 2, the first urine examination was performed and a reaction for protein was observed. When seen on August 4, the child had a protuberant abdomen, with ascites and anasarca. The blood pressure was 90/60, and results of physical examination were otherwise normal. Repeated examination revealed a high degree of proteinuria. There were only very rare casts, rare red blood cells and rare epithelial cells. On one occasion a typical blood cast was seen. The total serum protein concentration was 2.88 Gm. per 100 cc.; the hematocrit was 34 mm. (Wintrobe); the serum creatinine concentration was 0.88 mg. per 100 cc., and there was marked, obvious lipemia.

Because of increasingly severe edema and ascites, the child was admitted to the hospital and resin administration was initiated. The result can be seen in figure 2. With a dose of 8 Gm. four times a day, the initial weight of 44 pounds was rapidly reduced to 38 pounds. At this point, the child was lethargic and drowsy, with a diminution in the carbon dioxide-combining power, as indicated. Use of the resin was discontinued for two days. During this time there was no increase in weight, but the carbon dioxide-combining power returned to normal. Within 12 hours after discontinuance of the resin treatment the patient's behavior had returned to normal. Resin administration was then reinstituted, and in the course of seven more days the weight had diminished to 34 pounds (15.4 Kg.), with very slight edema and moderate ascites remaining. Since that time, the child has been maintained virtually free of edema and ascites by intermittent resin administration.

CASE 4.—L. G., a housewife, aged 49, known to have had diabetes mellitus for 12 years, was treated by diet and insulin administration. In late 1948 she was found to have edema of the legs, with pronounced proteinuria and hypertension and anemia. In September 1949 she had acute hepatitis following a transfusion. When examined in December 1949, the ocular fundi showed minimal changes of vascular sclerosis. Her blood pressure was 180/105. The liver was palpable just below the costal margin and was slightly tender on pressure. There was moderately severe edema of the legs, and no other significant abnormalities were seen. The urine contained large amounts of protein, many white and epithelial cells, red blood cells and occasional casts. A number of blood casts was seen. The serum creatinine concentration was 0.86 mg. per 100 cc. There was a mild anemia, with the hematocrit measuring 36 mm. (Wintrobe). The serum sodium concentration was 302 mg. and serum potassium 24 mg. per 100 cc. The carbon dioxide-combining power was 43.5 volumes per cent.

Occurrence and Treatment of Hypokalemia During Cation Exchange Resin Treatment (Case 4)

Date	3/28	3/29	3/30	3/31	4/1	4/2	4/3	4/4	4/5	4/6
Serum potassium, mg./100 cc.	13.0	11.0	10.1	9.1	14.5	...	...	...	...	21.8
Potassium given intravenously, Gm.	....	5.4	4.0	2.0	....	...	...	...	...	....
Potassium given orally, Gm.	1.0	1.0	1.0	3.0	3.0	3.0	3.0	3.0	3.0	....

She was given cation exchange resin, 8 Gm. four times a day, and responded well. She lost 25 pounds (11.3 Kg.) and reached a minimum weight of 150 pounds (68 Kg.) one month after treatment was started. After that resin was given intermittently in accordance with her weight. The afternoon of March 29, 1950 she was seen in the office at 1:00 p. m. and seemed well, but complained of a little weakness. Blood was drawn for various determinations. By 6:00 p. m., before the results could be obtained, she became disoriented and confused, with hyperpnea, and was admitted to the hospital. It was later found that in the blood taken at 1:00 p. m. the serum sodium concentration was 304 mg. and potassium 13 mg. per 100 cc., with a carbon dioxide-combining power of 20 volumes per cent. Acting on the probability that she was in hypokalemia and acidosis, she was given 5 per cent dextrose in 0.85 per cent saline solution intravenously, with administration of potassium chloride by mouth and by vein and of insulin to counteract the dextrose. The table shows the daily changes in her serum potassium level, together with the doses of potassium chloride that were given by mouth and by vein. Much larger doses were required to correct her electrolyte deficiency than were anticipated from the initial serum potassium concentration. With administration of adequate amounts, she improved rapidly and returned home in one week, feeling quite well.

SUMMARY

The cation exchange resin provides a useful means of relieving edema in the nephrotic syndrome. Because the ion exchange is not specific, patients must be observed carefully to detect the onset of acidosis and electrolyte deficiencies. With proper precautions, toxic effects can be avoided and, in most cases, the edema can be relieved. No effect has been observed on the natural course of the underlying disease.

BLOOD VOLUME IN PULMONARY TUBERCULOSIS

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THERE is only one report in the literature regarding the blood volume in pulmonary tuberculosis. Allbritten and co-workers,[1] using the Evans blue dye method, found that in 10 patients there was an average reduction in blood volume of approximately 15 per cent. These workers did not discuss the total red cell volume or plasma volume in their patients. Muller [2] in his monograph on the blood in tuberculosis discusses the red cell count, particularly from the standpoint of anemia. In general, in Muller's frequency diagrams, the means and range for the red blood cell count, hemoglobin concentration and hematocrit in patients with pulmonary tuberculosis, both male and female, are approximately the same as normal values, with the exception that the range is somewhat greater in patients with pulmonary tuberculosis. Also mentioned was the possibility that some patients may have secondary polycythemia, although no data regarding this were given.

The present study was carried out to measure the blood volume, total red cell volume and plasma volume in patients with pulmonary tuberculosis.

METHODS

The blood volume was determined in 26 adult patients with pulmonary tuberculosis by the use of P^{32} labeled red blood cells. The method was a modification [3] of that of Hevesy and

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1. Allbritten, F. F., Jr.; Lipshutz, H.; Miller, B. J., and Gibbon, J. H., Jr.: J. Thoracic Surg. **19**:71, 1950.

2. Muller, G. L.: Clinical Significance of the Blood in Tuberculosis, New York, The Commonwealth Fund, 1943.

3. (*a*) Berlin, N. I.; Huff, R. L.; Van Dyke, D. C., and Hennessy, T. G.: Proc. Soc. Exper. Biol. & Med. **71**:176, 1949. (*b*) Berlin, N. I.; Lawrence, J. H., and Gartland, J.: J. Lab. & Clin. Med. **36**:435, 1950.

Zerahn [4] for the in vitro labeling of red blood cells. All these patients had active pulmonary tuberculosis. All the patients had advanced or moderately advanced pulmonary tuberculosis, with signs of activity. Sixteen were candidates for various thoracic surgical procedures.

RESULTS

The results on determinations of blood volume, total red cell volume, plasma volume and hematocrit are recorded in the table. These show that, with the exclusion of patients 25 and 26, there was a reduction in the average total blood volume, in the average total red cell volume and in the average plasma volume, but no significant change in the hematocrit. It should be noted that in patients 25 and 26 the blood volume was considerably above normal, as was the total red cell volume, although the hematocrit readings were within the range of normal. In both these patients (25 and 26) the total red cell volume is such that it would

The Blood Volume in Pulmonary Tuberculosis

Females					Males				
Patient No.	Blood Volume *	Total Red Cell Volume *	Plasma Volume *	Hematocrit, %	Patient No.	Blood Volume *	Total Red Cell Volume *	Plasma Volume *	Hematocrit, %
1	49.8	21.9	27.9	44	15	60.3	27.7	31.9	46
2	40.9	16.4	24.5	40	16	56.3	20.8	34.9	37
3	40.7	14.6	25.6	36	17	59.4	29.7	29.7	50
4	47.8	21.8	26.5	46	18	72.6	29.8	41.8	41
5	47.3	19.4	27.9	41	19	40.8	16.3	24.5	40
6	61.9	27.9	33.7	45	20	59.3	25.5	33.2	43
7	59.9	25.7	33.5	43	21	52.9	23.8	28.6	45
8	49.1	19.6	28.9	40	22	70.6	30.3	37.6	43
9	57.5	23.0	33.9	40	23	55.8	25.1	30.1	45
10	52.9	24.4	28.1	46	24	77.8	33.1	43.6	42
11	69.1	24.1	44.0	35	..	....	....	....	..
12	57.6	23.0	34.6	40	..	....	....	....	..
13	54.6	22.4	32.2	41	..	....	....	....	..
14	67.0	24.1	42.2	36	..	....	....	....	..
Average	53.5	22.0	31.7	40.9	Average	60.58	26.2	34.0	43.2
Normal (16 cases)[7]	64.4	27.0	37.0	41.9	Normal (71 cases)[ab]	67.6	29.9	38.7	44.2
25	86.7	36.4	49.1	42	..	....	....	....	..
26	79.8	36.1	43.1	45	..	....	....	....	..

* Expressed in cubic centimeters per kilogram of body weight.

indicate that these patients showed polycythemia (red cell hypervolemia), which we believe to be secondary to pulmonary fibrosis.

COMMENT

Clark [5] and Gregersen [6] and their co-workers have shown that there is a reduction in blood volume in certain chronic debilitating diseases, but they made no study of patients with pulmonary tuberculosis. The studies reported here show that the blood volume is usually significantly reduced in chronic tuberculosis. Although some of these patients may have lost weight, the reduction in blood volume is greater than can be accounted for purely by loss of weight, since the

4. Hevesy, G., and Zerahn, K.: Acta physiol. scandinav. **4**:376, 1942.

5. Clark, J. H.; Nelson, W.; Lyons, C.; Mayerson, H. S., and Decamp, P.: Ann. Surg. **125**:618, 1947.

6. Gregersen, M. I.: J. Lab. & Clin. Med. **29**:1266, 1944.

figures are given in cubic centimeters per kilogram of body weight. In both males and females there is a reduction in the blood volume, total red cell volume and plasma volume. In the 10 male patients the average total red cell volume was 26.2 cc. per kilogram of body weight, as compared with a normal value of 29.9 cc. per kilogram of body weight (approximately a 12.4 per cent reduction). In the 14 female patients the average total red cell volume was 22.0 cc. per kilogram of body weight, as compared with a normal level of 27.0 cc. per kilogram of body weight [7] (approximately an 18.5 per cent reduction). In both males and females the plasma volume was also reduced. Although these patients have a normal concentration of red cells, as measured by the red blood cell count, hemoglobin concentration and hematocrit, they are actually anemic, since the total amount of red cells, hence the total capacity of the blood to carry oxygen, is reduced. As in other disease states, the hematocrit cannot be used to predict accurately the total red cell volume.[8]

This reduction in total red blood cell volume and blood volume has important implications in the general care and in the preparation of these patients for surgical procedures. In order to prepare these patients properly for major thoracic or other surgical operations, a sufficient number of transfusions of whole blood should be given to raise the total red cell volume at least to the normal level for their present body weight. This procedure has been shown to be desirable from a surgical standpoint.[9]

CONCLUSIONS

The blood volume was determined in 26 patients with pulmonary tuberculosis and was, on the average, found to be low.

Two of the patients showed an elevated blood volume and an elevated total red cell volume; in one there was an elevated plasma volume, but both showed normal hematocrit readings. In both these patients the pulmonary disease was such that secondary polycythemia could explain this phenomenon.

It is evident that the total red cell volume and the total blood volume cannot be predicted on the basis of the hematocrit (packed cell volume), red blood cell count or hemoglobin determination in pulmonary tuberculosis, as well as in other diseases.

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7. Berlin, N. I.; Hyde, G.; Parsons, R. J., and Port, S.: The Blood Volume in the Normal Female as Determined by P-32 Labeled Red Blood Cells, to be published.

8. Berlin and others.[3b] Berlin, N. I.; Lawrence, J. H., and Gartland, J.: Am. J. Med. **9**:747, 1950.

9. Berlin, N. I.; Rowles, D. F.; Hyde, G.; Parsons, R. J.; Samson, P. C., and Port, S.: The Blood Volume and Blood Turnover in Thoracic Surgery, Surg., Gynec. & Obst., 1951, to be published.

POTASSIUM DEFICIENCY IN CHRONIC RENAL DISEASE

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IN RECENT years much attention has been directed to the occurrence of potassium intoxication in renal disease.[1] Reports of intolerance to potassium in renal insufficiency [2] have contributed to the general impression that patients with damaged kidneys have decreased capacity to rid the body of potassium, that there is thus "retention" of potassium and that the patient with terminal renal disease dies as the result of cardiac intoxication secondary to hyperpotassemia.

It would appear, however, that derangement of potassium metabolism in renal disease will commonly result in the occurrence of potassium deficiency. It is true that some patients with advanced renal insufficiency may have an elevated serum potassium concentration and certain of these patients will demonstrate clinical or electrocardiographic evidence of potassium intoxication.[3] Many patients, however, will have normal or near-normal serum levels despite evidence of severe renal disease, and, indeed, this has been the more usual observation in this laboratory.[4] The

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This study was supported by a research grant from the National Institutes of Health, United States Public Health Service.

1. (*a*) Keith, N. M., and Burchell, H. B.: Clinical Intoxication with Potassium: Its Occurrence in Severe Renal Insufficiency, Am. J. M. Sc. **217**:1, 1949. (*b*) Bywaters, E. G. L.: Ischemic Muscle Necrosis: Crushing Injury, Traumatic Edema, Crush Syndrome, Traumatic Anuria, Compression Syndrome; Type of Injury Seen in Air Raid Casualties Following Burial Beneath Débris, J. A. M. A. **124**:1103 (April 15) 1944. (*c*) Finch, C. A., and Marchand, J. F.: Cardiac Arrest by Action of Potassium, Am. J. M. Sc. **206**:507, 1943. (*d*) Finch, C. A.; Sawyer, C. G., and Flynn, J. M.: Clinical Syndrome of Potassium Intoxication, Am. J. Med. **1**:337, 1946. (*e*) Marchand, J. F., and Finch, C. A.: Fatal Spontaneous Potassium Intoxication in Patients with Uremia, Arch. Int. Med. **73**:384 (May) 1944. (*f*) Stewart, H. J.; Shepard, E. M., and Horger, E. L.: Electrocardiographic Manifestations of Potassium Intoxication, Am. J. Med. **5**:821, 1948.

2. Winkler, A. W.; Hoff, H. E., and Smith, P. K.: The Toxicity of Orally Administered Potassium Salts in Renal Insufficiency, J. Clin. Invest. **20**:119, 1941. Hoff, H. E.; Smith, P. K., and Winkler, A. W.: The Cause of Death in Experimental Anuria, ibid. **20**:607, 1941. Winkler, A. W.; Hoff, H. E., and Smith, P. K.: Electrocardiographic Changes and Concentration of Potassium in Serum Following Intravenous Injection of Potassium Chloride, Am. J. Physiol. **124**:478, 1938. Keith, N. M., and Osterberg, A. E.: The Tolerance for Potassium in Severe Renal Insufficiency: A Study of 10 Cases, J. Clin. Invest. **26**:773, 1947.

3. (*a*) Footnote 1 *a, d to f*. (*b*) Elkinton, J. R.; Tarail, R., and Peters, J. P.: Transfers of Potassium in Renal Insufficiency, J. Clin. Invest. **28**:378, 1949.

4. (*a*) Leaf, A., and Camara, A. A.: Tubular Secretion of Potassium in Man, J. Clin. Invest. **28**:1526, 1949. (*b*) Newburgh, L. H.; Schoch, H. K.; Reimer, A., and Leaf, A.: Unpublished data.

demonstration of subnormal serum potassium concentration or the clinical evidence of potassium deficiency in such patients has not been uncommon in our experience; yet little attention has been paid this fact by others, and the literature contains relatively few reports of such occurrences.[5]

The significance of potassium deficiency may, perhaps, be more fully appreciated after recalling some of the basic facts of potassium metabolism in health and disease. In 1940 Fenn[6] exhaustively reviewed the subject of the physiological role of potassium, and several authors have more recently emphasized the importance of potassium in cellular metabolism.[7] Briefly, it appears that a specific intracellular content of potassium is essential for the proper functioning of certain enzymatic processes of the cell, notably those concerned with carbohydrate metabolism. Potassium plays a vital role, furthermore, in maintaining iso-osmotic equilibrium between the intracellular and extracellular fluids, as well as in the preservation of normal pH of body fluids through its potentialities as a buffer and in the establishment of the proper level of neuromuscular irritability. Certain of these functions are dependent on the maintenance of a normal concentration of potassium in the extracellular fluid, a level usually considered to be in the range of 3.5 to 5.0 milliequivalents per liter. Contrasting this with the intracellular concentration of 155 to 160 milliequivalents per liter, one is struck with the remarkable ability exhibited by the cell in maintaining such a difference in concentration on either side of a membrane which is, in fact, completely and freely permeable to potassium.

In the normal person total excretion of potassium closely parallels intake. All natural foods contain large amounts of potassium, and the ingestion of even small quantities of food will usually suffice to balance potassium excretion. Loss of potassium in the sweat is minimal under usual conditions.[8] The stool contains a moderate but fairly constant amount, which shows little change regardless of the variation in potassium content of the usual therapeutic diets. The chief route of excretion, however, is via the kidney, approximately 90 per cent of ingested potassium appearing in the urine.[9]

Certain disease states (notably diarrheal diseases, intestinal obstruction and diabetic ketosis), through associated acidosis, alkalosis and/or dehydration, have been shown to result in potassium deficiency, with partial replacement of the intra-

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5. Elkinton and others.[3b] Brown, M. R.; Currens, J. H., and Marchand, J. F.: Muscular Paralysis and Electrocardiographic Abnormalities Resulting from Potassium Loss in Chronic Nephritis, J. A. M. A. **124**: 545 (Feb. 26) 1944. Sherry, S.; Eichna, L. W., and Earle, D. P., Jr.: The Low Potassium Syndrome in Chronic Nephritis, abstracted, J. Clin. Invest. **27**:556, 1948.

6. Fenn, W. O.: The Role of Potassium in Physiological Processes, Physiol. Rev. **20**:377, 1940.

7. (*a*) Newburgh, L. H.: Significance of the Body Fluids in Clinical Medicine, Springfield, Ill., Charles C Thomas, Publisher, 1950. (*b*) Darrow, D. C., and Pratt, E. L.: Fluid Therapy: Relation to Tissue Composition and the Expenditure of Water and Electrolyte, Report of Council on Foods and Nutrition, J. A. M. A. **143**:306 (May 27); 432 (June 3) 1950. (*c*) Danowski, T. S.: Newer Concepts of the Role of Potassium in Disease, Am. J. Med. **7**:525, 1949.

8. Arn, K. D., and Reimer, A.: Minimal Sodium Losses Through the Skin, J. Clin. Invest. **29**:1342, 1950.

9. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. 1: Interpretations, Baltimore, Williams & Wilkins Company, 1931.

cellular potassium by sodium.[10] The potassium released by the cells passes into the extracellular fluid and is excreted in the urine unless renal function is nearly abolished. The nature of the underlying disease in these patients, or the accompanying anorexia or nausea, may preclude the ingestion of amounts of potassium sufficient to counterbalance total losses. Urinary losses continue, nevertheless, and the kidney can thus be said to play a major role [11] in the development of the serious intracellular potassium deficits which may occur.[12] If such deficit is severe, return of normal electrolyte balance and improvement in the clinical picture may depend heavily on the administration of potassium, orally or parenterally.

Such serious depletion of intracellular potassium stores is frequently accompanied with a fall in the concentration of serum potassium. The occurrence of a normal serum level, however, is not uncommon in these circumstances, and here the extent of intracellular potassium deficit can be estimated only by calculation of retention of orally or parenterally administered potassium.[13]

Much emphasis has been placed on what is termed the intolerance of patients with renal damage to the administration of potassium, and one is cautioned against the use of sizable quantities of potassium salts in such patients. Yet, not infrequently the situation arises when potassium must be administered, in the face of renal insufficiency, to patients in whom intracellular potassium deficit is known or suspected.

REPORT OF CASES

CASE 1.—D. M., a 49 year old white man, entered the hospital in uremia. The early hospital course was marked by stupor and convulsions. Pyelograms demonstrated polycystic kidneys.

Transfusions and infusions of saline, dextrose and sodium lactate solutions produced little improvement. Rapid recovery ensued after the addition of potassium to the fluids given intravenously. After 16 Gm. of potassium chloride had been administered, the serum potassium concentration was 3.2 milliequivalents per liter. Potassium bicarbonate was administered orally in the dosage of 12 Gm. daily, and the patient continued to improve. At discharge the serum potassium level was 7.7 milliequivalents per liter. Potassium administration was discontinued at this time.

During the next year, the patient was able to continue his usual activities and occupation. Serum potassium ranged from 6.3 to 7.3 milliequivalents per liter. The course prior to the final admission was marked by weakness and nausea. Blood chemical studies showed that dilution of the extracellular fluid had occurred. The serum potassium had fallen to about 5 milliequivalents per liter.

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10. (*a*) Darrow and Pratt.[7b] (*b*) Darrow, D. C.: Disturbances in Electrolyte Metabolism in Man and Their Management, Bull. New York Acad. Med. **24**:147, 1948. (*c*) Darrow, D. C.; Schwartz, R.; Iannucci, J. F., and Coville, F.: The Relation of Serum Bicarbonate Concentration to Muscle Composition, J. Clin. Invest. **27**:198, 1948. (*d*) Mudge, G. H., and Vislocky, K.: Electrolyte Changes in Human Striated Muscle in Acidosis and Alkalosis, ibid. **28**:482, 1949.

11. Tarail, R., and Elkinton, J. R.: Potassium Deficiency and the Role of the Kidney in Its Production, J. Clin. Invest. **28**:99, 1949.

12. Govan, C. D., Jr., and Darrow, D. C.: The Use of Potassium Chloride in the Treatment of the Dehydration of Diarrhea in Infants, J. Pediat. **28**:541, 1946.

13. Govan and Darrow.[12] Darrow, D. C.: The Retention of Electrolyte During Recovery from Severe Dehydration Due to Diarrhea, J. Pediat. **28**:515, 1946. Atchley, D. W.; Loeb, R. F.; Richards, D. W., Jr.; Benedict, E. M., and Driscoll, M. E.: On Diabetic Acidosis: A Detailed Study of Electrolyte Balances Following the Withdrawal and Reestablishment of Insulin Therapy, J. Clin. Invest. **12**:297, 1933.

Balance studies during the final hospitalization showed retention of administered potassium coincident with temporary improvement in the clinical picture, particularly in relief of semistupor and disorientation. With progressive oliguria, the serum potassium level rose to 9.0 milliequivalents per liter. Autopsy confirmed the diagnosis of polycystic kidneys.

Comment.—This patient with advanced renal insufficiency was in definite potassium deficit when first seen, the serum concentration (which was not obtained until after several days of intravenous potassium administration) having been 3.2 milliequivalents per liter. When his body stores of fixed base were finally brought to normal, the serum potassium level was definitely elevated (7.7 milliequivalents per liter) and remained above 6 milliequivalents per liter until one month prior to death. At the time of this patient's last admission, there again was potassium deficit, as evidenced by a serum potassium level abnormally low for this patient, by retention of administered potassium and by improvement in the clinical picture when potassium was administered.

During the last two weeks of life, measurement of intake and urinary output of sodium, potassium and nitrogen provided data for a roughly quantitative balance study. Dietary intake of potassium was sufficient to balance urinary excretion despite decreased intake of food. There was present, however, a preexisting potassium deficit of such magnitude that the major portion of the potassium administered (in addition to the content of the diet) was retained. Less than 100 milliequivalents of the 325 milliequivalents of potassium retained was utilized in achieving the final elevation of serum potassium concentration.

Case 2.—F. W., a 27 year old white man, had been observed for nearly two years, during which time he entered the hospital on many occasions. Glomerulonephritis had been diagnosed nine years previously. Albuminuria was pronounced, and a serious degree of hypertension caused many episodes of cardiac failure. Ascites and edema recurred repeatedly.

The serum potassium concentration was 4.0 milliequivalents per liter when first determined (January 1949) and remained within normal limits (except for the occasion mentioned below) for the next six months. Then, during the last three months of life, there was a gradual rise from 6.0 to 7.9 milliequivalents per liter on the day of death.

In March 1949, after a week of nausea and vomiting, the serum potassium concentration was found to be 2.8 milliequivalents per liter. There were no symptoms at this time attributable to the hypopotassemia. After several days of hospitalization the serum level was 3.5 milliequivalents per liter. During this time, the patient had eaten his usual diet and no additional potassium had been administered.

Six months later, oliguria developed and after three days of anuria the serum concentration of potassium was 7.9 milliequivalents per liter. Autopsy demonstrated the typical findings of chronic glomerulonephritis.

Comment.—The reduced intake of potassium, together with continuing loss of potassium averaging 30 to 35 milliequivalents daily, may be implicated in the development of the isolated instance of hypopotassemia seen here. On the day that the hypopotassemia was present, renal tubular secretion of potassium was continuing (see general comment and table) and this mechanism definitely contributed to the development of the low serum level. It is significant that hypotassemia was present despite the presence of renal damage of such magnitude that the glomerular filtration rate was less than 5 per cent of normal.

Case 3.—D. P., a 37 year old white woman, had been observed during the course of progressive glomerulonephritis for nearly six years. When she was first seen, the serum protein concentration was low and massive edema was present.

The serum potassium concentration during the last six months of life was within normal limits until the final admission. For one week before admission to the hospital there had been continual nausea and vomiting, and the patient appeared dehydrated, stuporous and in terminal convulsions. The serum potassium level at this time was 3.0 milliequivalents per liter. During the next 24 hours, approximately 50 milliequivalents of potassium was administered in the fluids given intravenously and this resulted in a rise in the serum potassium level to 4.3 milliequivalents per liter. During this 24 hour period, the urinary excretion of potassium was 38.4 milliequivalents. The patient died on the following day, and autopsy demonstrated the findings of active chronic glomerulonephritis.

Comment.—This case, likewise, demonstrates the importance of nausea and vomiting in the acute production of potassium deficit, as a result of decreased intake, dehydration and continuing urinary losses. Again, low serum potassium levels developed despite severe renal insufficiency. It is possible that earlier administration of potassium might have resulted in a life-saving relief of the potassium deficiency, since this patient's situation closely paralleled that of the first patient (case 1) at the time of his first admission.

Summary of Data on Patients with Potassium Deficiency in Renal Disease

Patient	Date	Serum Potassium Level, mEq./L.	G. F. R.,* L./24 Hr.	Filtered Potassium,† mEq./24 Hr.	Excreted Potassium,† mEq./24 Hr.
D. M.	3/ 3/49	7.7	6.6	50.8	84.2
F. W.	2/18/49	5.3	4.0	21.2	31.4
F. W.	3/15/49	2.8	7.2	20.2	30.3
D. P.	5/11/49	3.8	9.9	37.6	45.2

* G. F. R. is glomerular filtration rate as estimated by endogenous creatinine clearance.

† Filtered potassium represents the amount of potassium appearing in the urine which could be accounted for on the basis of total glomerular filtration alone. Excreted potassium is the total amount appearing in the urine during the same 24 hour period. The difference between excreted and filtered potassium gives a measure of the amount which reached the urine through secretion by the renal tubules.

GENERAL COMMENT

In the light of present knowledge the daily minimal loss of potassium amounts to approximately 20 to 25 milliequivalents, of which perhaps 15 milliequivalents appears in the urine. Evidence is not available concerning the ability of the normal or diseased kidney to maintain potassium balance in the person who is in nitrogen balance and whose only dietary restriction is that of potassium.[14] There is suggestive evidence, however, that the diseased kidney conserves potassium less efficiently than does the normal kidney—just as has been shown to be the case with sodium.[7a] Recent work by Burrows and associates[15] demonstrated almost constant urine volumes and urine concentrations of electrolytes (potassium in particular) in patients with advanced renal disease, despite controlled variation in intake of electrolytes,

14. Thus far, adequate investigation of a low potassium intake in the human subject has depended on the withholding of food, with the subject in negative nitrogen balance. A more accurate representation of tubular capacity to reabsorb potassium would be found in the situation where the subject is offered a diet low in potassium but adequate in protein and calories. Such an investigation is under way in this laboratory at present. Preliminary results suggest that the normal kidney is unable to conserve potassium adequately in these circumstances (Reimer, A.; Hewitt, H. C., and Newburgh, L. H.: Unpublished data).

15. Burrows, B. A.; Commons, R. R., and Burnett, C. H.: Sodium and Potassium Excretion in Patients with Renal Insufficiency, Am. J. Med. **7**:423, 1949.

the result being a fairly constant excretion of electrolytes. The urinary electrolyte concentrations in these patients were much higher than those observed in normal subjects with minimal urine volumes. Similar observations have been made in this laboratory.[16] The investigations of other workers [17] have also led to the conclusion that the patient with renal damage shows a lessened ability to retain potassium.

In this regard, it is an interesting observation that renal tubular secretion of potassium, a mechanism which mitigates hyperpotassemia through "compensation" for reduced glomerular filtration, may well contribute to excessive loss of potassium in the urine. Tubular secretion seems to continue functioning whether the serum potassium level is high, normal or low.[4a] This certainly contributed to the hypopotassemia seen in the case of F. W. (table) and probably was of importance in the production of the low serum levels evidenced by D. M. early in the course of his first hospital admission and by D. P. at the time of her last admission.

We may thus tentatively conclude that potassium deficiency is due, in part, to changes in secretory and resorptive functions of the renal tubules.

As the degree of renal insufficiency advances, there is progressive impairment of the renal mechanisms acting to rid the body of excess quantities of acid ions. In the normal situation these acid ions are, in part, excreted as the acid itself in amounts limited by the inability of the renal tubules to produce urine more acid than pH 4.5.[18] This mechanism plays an important role in conservation of fixed base when large quantities of organic acids or phosphates must be removed. Renal tubule cells are also capable of the production of ammonia from circulating amino acids in amounts up to 400 milliequivalents daily in the normal person.[7a] The ammonium ion thus formed is available for excretion in company with the acid ions. When quantities of the stronger acid ions (chloride and sulfate) must be excreted, the manufacture of ammonia is the major base-saving mechanism involved. As the above discussion implies, a certain amount of fixed base must always be excreted (in addition to ammonia production and the "titrable acidity" mechanism) in the "balancing" of excreted acid ions, and, in the normal situation, this excretion of fixed base exhibits a nicety of adjustment such that excretion of base balances the intake. Ammonia production and the "titrable acidity" mechanism will thus increase in response to demands for conservation of fixed base, or decrease in the event of the occasional need for excretion of excess quantities of fixed base.[19]

With decrease in capacity for ammonia production and with reduction in the ability to produce an acid urine, it is evident that increased excretion of fixed base must result whenever large quantities of acid ions are presented to the kidney for excretion (for example, when acid salts such as ammonium chloride are administered). Usually the fixed base lost consists primarily of sodium.[20] An appreciable

16. Schoch, H. K.; Reimer, A., and Camara, A. A.: Unpublished data.

17. Elkinton and others.[3b] Tarail and Elkinton.[11]

18. Pitts, R. F.; Lotspeich, W. D.; Schiess, W. A., and Ayer, J. L.: The Renal Regulation of Acid-Base Balance in Man: I. The Nature of the Mechanism for Acidifying the Urine, J. Clin. Invest. **27**:48, 1948.

19. Pitts, R. F.; Ayer, J. L., and Schiess, W. A.: The Renal Regulation of Acid-Base Balance in Man: III. The Reabsorption and Excretion of Bicarbonate, J. Clin. Invest. **28**:35, 1949.

20. Gamble, J. L.; Blackfan, K. D., and Hamilton, B.: A Study of the Diuretic Action of Acid Producing Salts, J. Clin. Invest. **1**:359, 1925.

amount of potassium is excreted in such a situation, however, and the fixed base excreted during ammonium chloride administration may consist almost entirely of potassium when there exists an intense stimulus to the kidney to conserve sodium.[21] Intracellular potassium (designated by Darrow [10b] as an important buffer in acidosis) is thus depleted as potassium, in response to the body's demand for conservation of sodium, leaves the cells and is excreted in the urine as a substitute for sodium.

Of perhaps greater clinical importance is the fact that the person with advanced renal damage will lose greater than normal quantities of fixed base in the excretion of the acid end products (phosphates and sulfates) resulting from the metabolism of the quantity of protein ingested in the usual diet. Again, the results are more apparent in those persons faced with the need for unusual conservation of base, for example, the "salt-losing" nephritic.[22]

When urinary losses of potassium continue to be large either as the result of decreased functional capacity or because of the necessity for excreting large quantities of acid ions, adequate intake of potassium becomes all-important in the maintenance of potassium balance. The clinical situation, then, where potassium deficiency is to be anticipated is in the case of the patient with severe renal insufficiency who is unwilling or unable to eat even the most modest diet. The anorexia, nausea and persistent vomiting that are so common in the later stages of renal disease thus contribute decidedly to the development of potassium deficiency by reducing dietary intake of potassium.

The symptomatic picture presented by the patient in potassium deficiency is not clearcut. General weakness and hypotonia of the skeletal muscles are often the only signs. Occasionally, paralysis of the muscles of the extremities is seen. Electrocardiographic findings have been of little value, in our experience, largely because of the nonspecificity of the changes and the masking of such changes by other abnormalities in the electrolyte pattern.

The time required for potassium deficiency to become clinically apparent must vary widely and will depend on such factors as the degree of negative potassium balance and the extent of functional impairment of the kidneys, as well as on the state of the body stores of potassium, normally a considerable quantity (more than 5,000 milliequivalents).

Rational attempts at therapy must be aimed at assuring an adequate intake of potassium, reducing the quantity of acid ions presented for excretion and restoring normal intracellular and extracellular content of potassium when depletion has occurred.

Protein-restricted diets as used in chronic renal insufficiency [23] contain a daily minimum of 40 to 50 milliequivalents of potassium. With the anorexia and nausea of advanced renal disease, it is apparent that the dietary intake of potassium may average considerably less than this figure. It is thus important to devise a varied, attractive and adequate diet, and here close cooperation among the physician, the

21. Schoch and others.[16] Gamble and others.[20] Sartorius, O. W.; Roemmelt, J. C., and Pitts, R. F.: The Renal Regulation of Acid-Base Balance in Man: IV. The Nature of Renal Compensations in Ammonium Chloride Acidosis, J. Clin. Invest. **28**:423, 1949.

22. Thorn, G. W.; Koepf, G. F., and Clinton, M., Jr.: Renal Failure Simulating Adrenocortical Insufficiency, New England J. Med. **231**:76, 1944.

23. Addis, T.: Glomerular Nephritis: Diagnosis and Treatment, New York, The Macmillan Company, 1949.

dietitian and the patient's family becomes essential. Since the inexorable daily urinary loss of potassium in renal disease may average 40 to 50 milliequivalents [24] or more, it is necessary to regard this figure as the absolute minimum for daily intake of potassium. Oral supplements of potassium bicarbonate may be necessary to attain such an intake.

If the diet is adequate in calories and contains only that amount of protein necessary to maintain nitrogen balance, the quantity of acid phosphate and sulfate ions presented to the kidney for excretion will be reduced to a minimum, resulting in a decreased necessity for excretion of fixed base and ultimately conserving body stores of potassium. In this regard, there is good evidence, reviewed by Addis,[23] that 0.5 Gm. of protein per kilogram of body weight will be sufficient to maintain nitrogen balance in the adult.

Frequently, there will be periods when it is necessary to sustain the patient by parenteral administration of water, electrolytes and dextrose. In such an event, it is of the utmost importance to avoid potassium deficiency. Potassium chloride may be administered parenterally if no food is retained. Four to six grams daily distributed in 2 or 3 liters of dextrose or saline solution will usually suffice to maintain potassium balance and will assist in restoring deficit if this has occurred.

Appreciation of the various factors influencing potassium exchange and recognition of intracellular deficit, together with attempts at correction, are important features in the skilful management of the patient with chronic progressive renal disease. By such means, it is possible to extend the useful working life of the patient and keep him relatively comfortable and happy despite laboratory evidence of renal insufficiency of severe degree.

SUMMARY AND CONCLUSIONS

Potassium deficiency has been found to be a rather frequent occurrence in severe chronic renal disease.

In renal disease tubular secretion of potassium and the mechanisms for adjustment to acidosis may lead to excessive loss of potassium, while anorexia and nausea contribute to negative potassium balance by decreasing dietary intake.

Therapy should be preventive through assuring adequate intake of potassium and through reducing the quantity of acid ions presented to the kidney for excretion.

Where potassium deficiency exists, corrective therapy with oral or parenteral administration of potassium is indicated.

24. Elkinton and others.[3b] Tarail and Elkinton.[11] Schoch and others.[16]

HUMAN ADRENAL CORTEX AFTER ADMINISTRATION OF ACTH AND CORTISONE

Morphologic Changes

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THE INCREASING availability of pituitary adrenocorticotropic hormone (ACTH) and cortisone for clinical use has afforded us the opportunity to examine the adrenal glands of patients who had received these preparations prior to death. The possibility of finding structural changes which might be interpreted as a morphologic expression of functional stimulation or depression of the adrenal cortex made this study of interest. In addition, information might be obtained through which alterations in the adrenal glands of man could be compared with the known morphologic patterns in the adrenal cortices of animals under varying experimental conditions.

To appreciate the morphologic changes in the adrenal glands of patients studied in this series, it is necessary to review briefly the normal histologic pattern of lipid deposition in the human adrenal cortex. The greatest concentration of sudanophilic material is usually seen in the outer portion of the zona fasciculata, with a smaller amount in the zona glomerulosa and still less in the reticular and inner fascicular layers.[1] The significance of the localization of lipids is based on histochemical observations indicating that parallelism exists between the distribution of cholesterol and the degree of concentration of sudanophilic substance.[2] Sudan-stained lipids give some indication of storage and secretion of adrenal cortical hormones or their precursors and, as such, serve as an index of cortical activity. However, it should be realized that factors other than the adrenocorticotropic activity of the pituitary body may influence the concentration of sudanophilic materials.[2b]

METHODS AND MATERIAL

The material used in this report was taken from the necropsy services of the University Hospital and St. Joseph's Mercy Hospital, Ann Arbor, Mich. Blocks of tissue for microscopic

The work of Dr. Fajans was done during the tenure of a Life Insurance Medical Research Fellowship.

From the Department of Pathology (Drs. O'Donnell and Weinbaum) and the Department of Internal Medicine (Dr. Fajans), University of Michigan.

1. Sarason, E. L.: Adrenal Cortex in Systemic Disease: Morphologic Study, Arch. Int. Med. **71**:702-712 (May) 1943.

2. (*a*) Sarason.[1] (*b*) Sayers, G.: The Adrenal Cortex and Homeostasis, Physiol. Rev. **30**:241-320 (July) 1950.

examination were selected from the midportion of each adrenal gland of patients who had received either ACTH or cortisone. Frozen sections were stained with sudan III and paraffin sections with hematoxylin and eosin. The sections examined are believed to be representative of the respective adrenal glands, since the morphologic pattern was approximately the same for each of the adrenal glands in a given patient.

MICROSCOPIC OBSERVATIONS ON ADRENAL GLANDS OF PATIENTS WHO HAD RECEIVED ACTH

Table 1 contains the essential information on nine patients with respect to clinical diagnoses, total dosage of ACTH, duration of ACTH therapy and the interval between the last dose and necropsy.

There were no discernible changes in the structure of the adrenal glands in case 1. In case 2 a definite reduction of lipids and slight hypertrophy of the cells in the outer portion of the zona fasciculata were observed. No changes were seen

TABLE 1.—*Pertinent Data Concerning Patients Who Had Received ACTH*

Case No.	Sex	Age	Necropsy No.	Dosage, Mg.	Duration of Therapy, Days	Interval in Days Between Last Dose of ACTH and Necropsy	Clinical Diagnosis
1	M	62	A- 24-BC	40	1 (2 doses)	0	Bronchial asthma
2	F	48	A-317-BC	140	1½	0	Organic brain syndrome
3	M	39	A-183-BC	405	4	0	Bronchial asthma; gastrointestinal hemorrhage
4	M	37	A- 8 -BC	425	7	1	Xanthomatous biliary cirrhosis
5	M	42	A-237-BC	3,785	10	0	Second and third degree burns of body
6	F	28	A-352-BB	2,825	22	5	Subchronic myeloid leukemia
7	F	33	A-265-BC	1,550	17	10	Acute subleukemic monocytic leukemia
8	F	36	A-247-BC	650	7	23	Acute monocytic leukemia
9	F	72	50-2658	95	1 (3 doses)	0	Gangrenous diverticulitis and proctitis; granulocytopenia

in the zona glomerulosa or zona reticularis. In case 3 of this group the alteration was limited to a reduction of sudanophilic substance in the outer portion of the zona fasciculata. In case 4 there was great reduction of stainable lipids in all zones, and the remaining sudanophilic material was in the form of fine secretory granules. In addition, the cells of the fascicular zone were hypertrophic. In the patient (case 5) who had received the largest total dosage of ACTH the loss of sudanophilic material was quite apparent in all layers of the cortex, with only a few aggregations of lipid granules remaining in the zona glomerulosa. There was marked hypertrophy of the cells in the fascicular and reticular layers (fig. 1). Most of the cortex was composed of fascicular cells which had nonvacuolated, nonhoneycombed eosinophilic cytoplasm. The zona glomerulosa appeared to be narrow and poorly defined. At some levels this layer was of the usual width, but the greater part of it was reduced to one layer of cells. In case 6[3] there was a five day interval

3. This case was reported previously (O'Donnell, W. M., and Fajans, S. S.: The Adrenal Cortex Following ACTH: A Preliminary Report, Univ. Mich. M. Bull. **16**:169-172 [July] 1950).

between the last dose of ACTH and necropsy. In these adrenal glands the zona glomerulosa was prominent. Most of its cells appeared hypertrophic and contained abundant lipids. The cells of the zona fasciculata and zona reticularis were lipid poor. In the outer portion of the fascicular layer the cells were hypertrophic, and there was a tendency to form irregular masses. Clusters of proliferating cortical cells were seen in the capsule, and the larger aggregations formed discrete nodules. In case 7, with an interval of 10 days between the last dose of ACTH and death,

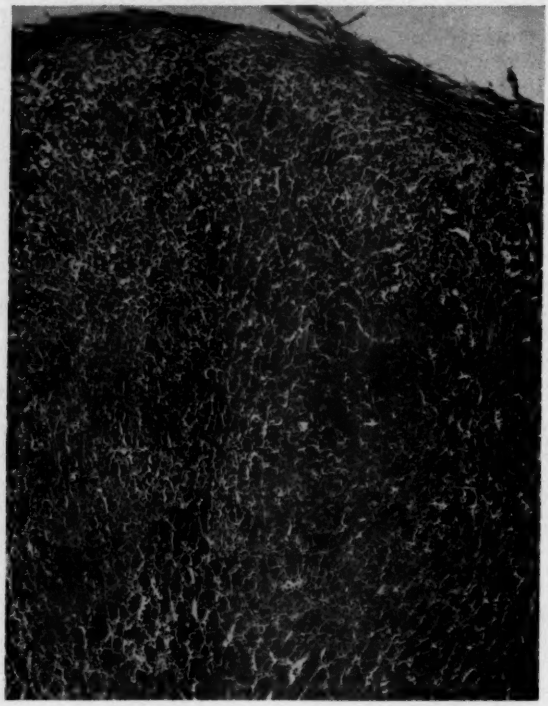

Fig. 1 (case 5, ACTH group).—Adrenal gland. Photomicrograph of the adrenal cortex illustrating the marked hypertrophy of the cells in the zona fasciculata and zona reticularis after administration of ACTH. The individual cells have nonvacuolated, nonhoneycombed eosinophilic cytoplasm. Hematoxylin and eosin stain; × 56.

the zona glomerulosa appeared to be of the usual width. There were clumps of hypertrophic cells in the outer portion of the zona fasciculata. No definite changes in cell size were observed in the inner part of the fascicular or reticular zones. Clusters of cortical cells, as well as discrete nodules, were seen in the capsule. Although the lipids were of reduced concentration, fine sudanophilic droplets were present in the fascicular and reticular layers. The adrenal glands in case 8 were examined 23 days after cessation of ACTH therapy. Hypertrophy of the fascicular

cells and narrowing of the zona glomerulosa were noted. Sudanophilic substance was in the form of fine secretory granules. Finally, in case 9 there was pronounced hypertrophy of the cells in the fascicular and reticular layers, and the capsule contained nodules of proliferating cortical cells. The zona glomerulosa was narrowed, but isolated nests of hypertrophic cells were observed in this layer. Abundant lipids were seen in all zones of the cortex.

An additional patient, data on whom are not included in table 1, had received 480 mg. of ACTH over a period of three days approximately six months before death. No unusual changes were noted in the adrenal glands.

Table 2 contains the essential information regarding the five patients who received cortisone.

MICROSCOPIC OBSERVATIONS ON ADRENAL GLANDS OF PATIENTS WHO RECEIVED CORTISONE

In the adrenal glands in case 10 there was marked atrophy of the cells in the zonae fasciculata and reticularis (fig. 2). Abundant brown pigment was observed

TABLE 2.—*Pertinent Data Concerning the Patients Who Had Received Cortisone*

Case No.	Sex	Age	Necropsy No.	Dosage, Mg.	Duration of Therapy, Days	Interval in Days Between Last Dose of Cortisone and Necropsy	Clinical Diagnosis
10	F	28	A-436-BB	2,175	21	0	Acute disseminated lupus erythematosus
11	F	32	A-218-BC	3,300 *	28	2	Lupus erythematosus disseminata
12	F	15	51-93	6,400	105	0	Lupus erythematosus disseminata; miliary tuberculosis
13	M	36	A-17-BC	1,050	12	17	Generalized scleroderma
14	M	63	51-122	6,000	31	51	Multiple myeloma; bronchopneumonia

* This patient had received 3,925 mg. of cortisone over a period of 3½ months ending one month before the initiation of the therapy noted here.

in the cells of the reticular layer. The zona glomerulosa was broadened and occupied almost half the diameter of the cortex. Although the concentration of sudanophilic material was reduced in frozen sections stained for fats, some lipid was seen in all layers, either as secretory granules or as large intracellular globules. In case 11, also, the marked atrophy was limited to the inner cortical layers (fascicular and reticular layers), and again the zona glomerulosa was broadened. The concentration of stainable adrenal lipids was less than that seen in case 10, but some fine granules and globules were distributed in all zones.

In case 12 there were slight broadening of the zona glomerulosa and extreme atrophy of the inner cortical layers. Many of the cells in the zona reticularis were in varying stages of necrosis. Again there was definite reduction in the lipid concentration, and the remaining lipids were localized in the glomerular and reticular layers. The adrenal glands in case 13, which were observed 17 days after cortisone administration was discontinued, showed slight atrophy in the outer portion of the fascicular layer. This retrogressive change was more definite in the inner part of

the zona fasciculata and in the zona reticularis. The zona glomerulosa was broadened. Cortical lipids were present in all zones as fine granules, but the concentration was reduced in the outer half of the zona fasciculata. Finally, in case 14, in which the interval between cortisone administration and examination was 51 days, the zona glomerulosa appeared to be of normal width. Cells of both fascicular and reticular layers were hypertrophic, and lipid reduction was marked in all parts of the cortex.

Fig. 2 (cases 10, cortisone group).—Adrenal gland. Photomicrograph of the adrenal gland showing the marked atrophy of cells in the zona fasciculata and zona reticularis after cortisone administration. The zona glomerulosa is broadened and occupies about half the cortex. Hematoxylin and eosin stain; × 56.

COMMENT

From the adrenal glands which we have examined it appears that the earliest morphologic response of the human adrenal cortex to ACTH is the reduction of sudanophilic substance and hypertrophy of the cells in the outer portion of the zona fasciculata. More prolonged stimulation leads to reduction of lipids in the other layers of the cortex. Lipid depletion associated with hypertrophy of cortical cells may be interpreted as increased secretory activity of the adrenal cortex. With

continued stimulation by adrenocorticotropic hormone, there are even greater loss of lipids in all zones and marked hypertrophy of cells in the fascicular and reticular zones. At this stage the zona glomerulosa is ill defined, of varying width and generally less prominent than in the normal adrenal gland. Some of the individual cells of this layer are of normal size; others appear to be hypertrophic. The reduction in width of the zona glomerulosa might be explained in either of two ways: 1. Hypertrophy of the zonae fasciculata and reticularis may cause a shrinkage of the zona glomerulosa by mechanical compression. 2. With increased secretory activity, stimulated by ACTH, there may be a more rapid transformation of cells of the zona glomerulosa to the fascicular type. Cells of the zona glomerulosa may normally be precursors of the secretory cells in the fascicular layer. The latter interpretation gains some support from the observation that many of the cells in the glomerulosa layer were hypertrophic. It has been shown in animal experiments that the zonae fasciculata and reticularis can regenerate from individual glomerulosa cells.[4]

A species difference may exist in the response of the adrenal cortex to pituitary influence. Some investigators [5] have postulated that the zona glomerulosa of the rat is not under pituitary control. On the other hand, the zona glomerulosa of the mouse [6] and that of the dog [7] have been observed to be influenced by adrenocorticotropin. Our observations lead us to believe that the zona glomerulosa of man is stimulated by ACTH.

The alarming stimulus of various types of stress may produce morphologic changes in the human adrenal cortex similar to those described in patients who were receiving ACTH at the time of death. Selye [8] listed certain diseases in which adrenal cortical hypertrophy and loss of lipid material have been described. These include burns, infectious diseases, intoxications with various drugs, bacterial toxins, exposure to x-rays, anoxia and transection of the spinal cord. Sarason [1] has noted similar findings in cachexia, pemphigus and protracted vomiting.

One patient (case 9) treated with ACTH had gangrenous diverticulitis and proctitis in addition to granulocytopenia. Ninety-five milligrams of ACTH given on the day of death cannot be responsible for the degree of cortical hypertrophy and hyperplasia seen in the adrenal glands of this subject. It is believed that the gangrenous inflammatory process and other secondary factors may have produced a sufficiently stressing situation to account for the adrenal changes on the basis of an endogenous alarm reaction. The abundant cortical lipids in association with

4. Zwemer, R. L.; Wotton, R. M., and Norkus, M. G.: A Study of Corticoadrenal Cells, Anat. Rec. **72**:249-263 (Oct.) 1938. Williams, R. G.: Studies of Adrenal Cortex: Regeneration of the Transplanted Gland and the Vital Quality of Autogenous Grafts, Am. J. Anat. **81**:199-213 (Sept.) 1947. Greep, R. O., and Deane, H. W.: Histological, Cytochemical and Physiological Observations on the Regeneration of the Rat's Adrenal Gland Following Enucleation, Endocrinology **45**:42-56 (July) 1949.

5. Bergner, G. E., and Deane, H. W.: Effects of Pituitary Adrenocorticotropic Hormone on the Intact Rat, with Special Reference to Cytochemical Changes in the Adrenal Cortex, Endocrinology **43**:240-260 (Oct.) 1948.

6. Jones, I. C.: The Relationship of the Mouse Adrenal Cortex to the Pituitary, Endocrinology **45**:514-536 (Nov.) 1949.

7. Ham, A. W.: Histology, Philadelphia, J. B. Lippincott Company, 1950.

8. Selye, H.: The General Adaptation Syndrome and the Diseases of Adaptation, J. Clin. Endocrinol. **6**:117-230 (Feb.) 1946.

pronounced cortical hypertrophy suggest a gradual and progressive stimulation rather than the relatively acute alteration which might be expected after one day of ACTH administration.[2b]

Again in case 8, in which death occurred 23 days after the last dose of ACTH, the marked cortical hypertrophy and lipid loss may have been due to stress rather than to a residual effect of exogenous ACTH. In patients who received larger doses of ACTH for longer periods and in whom the interval between the last dose of ACTH and the time of death was short, the cortical changes may be attributed to the exogenous ACTH, since it is known that ACTH administration depresses the secretion of endogenous adrenocorticotropic hormone. However, should the tissue demand for adrenocortical hormones exceed the amount elaborated by the adrenal glands with exogenous ACTH administration, secretion of endogenous adrenocorticotropic hormone might also be elicited. In such circumstances the changes in the adrenal cortex may be the result of a synergistic effect of exogenous and endogenous ACTH.

The adrenal morphologic changes induced by cortisone are very different from those produced by ACTH. Prolonged administration of cortisone caused atrophy of the zona fasciculata and zona reticularis. On the other hand, the zona glomerulosa appeared broadened, and its cells were of normal size. Sudanophilic substance, although of reduced concentration, was present in the cortex as intracellular globules and to a lesser degree as fine granules. The accumulation of lipid material in conjunction with cellular atrophy in the inner cortex may be regarded as evidence of storage of adrenal steroids or their precursors.

The alterations produced in the adrenal cortex after cortisone administration are similar to those seen in patients who had clinical and necropsy evidence of hypopituitarism. The adrenal glands examined for comparison with the cortisone series were those of persons who had destruction of their pituitary glands by advanced chromophobe adenomas or extensive necrosis as a result of postpartum infarction. The similarity of adrenal morphologic changes in cases of anterior pituitary insufficiency and in cases after cortisone administration suggests that cortisone induces adrenal atrophy by suppressing the secretion of pituitary adrenocorticotropic hormone. Sprague, Power and Mason[9] had previously made this observation. The atrophy described was confined to the fascicular and reticular zones. The cells of the glomerulosa layer were not atrophic. These cells, although under the influence of adrenocorticotropic hormone, may be able to survive with decrease or absence of secretion of this hormone. The broadening of the zona glomerulosa may be explained on the basis of a realinement of its cells because of the atrophic alteration and shrinkage of the inner cortex. A lessened demand for the transformation of glomerular to fascicular cells may be an additional contributing factor.

In the patient (case 13) who had not received cortisone for 17 days prior to necropsy, there was evidence showing the reversibility of atrophy and functional depression, since the cells of the outer fasciculata were in the process of reverting to normal size and the lipids were in a secretory pattern. Additional support for

9. Sprague, R. G.; Power, M. H., and Mason, H. L.: Physiological Effects of Cortisone and Pituitary Adrenocorticotropic Hormone (ACTH) in Man, J. A. M. A. **144**:1341-1347 (Dec. 16) 1950.

this observation is obtained from case 14, in which there was an interval of 51 days between cortisone therapy and death. The cortical hypertrophy and lipid loss seen in these adrenal glands are evidence that the influence of cortisone on the adrenal glands is reversible, and that these adrenal glands were able to respond to stress.

For a given person, the morphologic pattern of the adrenal cortex resulting from administration of ACTH or cortisone will depend on the preceding functional state of the cortex, total dosage of the preparation employed, interval between injections, duration of therapy and interval between cessation of administration and death. Possible variation in individual response of the adrenal glands may also have to be considered.

SUMMARY

The structural changes in the adrenal glands of patients who had received pituitary adrenocorticotropic hormone (ACTH) or cortisone before death were observed in 14 cases.

In those patients who had been given ACTH, there occurred loss of lipids, hypertrophy of the zona fasciculata and zona reticularis and, in some cases, cortical hyperplasia. The zona glomerulosa appeared narrowed and ill defined, but some of its cells were hypertrophic. This layer may have responded to the hormonal stimulation by a more rapid transformation of its cells to the fascicular type as a means of augmenting the secretory complex. The morphologic pattern in the adrenal glands of patients receiving ACTH is believed to be similar to that observed in patients who have been subjected to stress.

The adrenal glands of patients who had received cortisone showed marked atrophy of the fascicular and reticular layers and broadening of the zona glomerulosa. Although the sudanophilic material was reduced in concentration, some was still present as intracellular globules. These observations can be compared to the changes seen in the adrenal glands of persons in whom there has been destruction of the pituitary gland. This suggests that cortisone administration induces adrenal atrophy by suppressing the secretion of pituitary adrenocorticotropic hormone.

Dr. Stacy C. Howard, pathologist at St. Joseph's Mercy Hospital, Ann Arbor, Mich., permitted use of material from his laboratory.

PERITONEOSCOPIC CHOLANGIOGRAPHY

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INJECTION of radiopaque material into the gallbladder under peritoneoscopic vision affords a unique means of examining this organ and its ductal system roentgenographically. Lee [1] reported the procedure and recommended its use in cases in which the gallbladder could not be opacified by either the oral or the intravenous route. Hodges [2] cited one case in which this technique was utilized. Royer and Solari,[3] in an article devoted specifically to this subject, recommended its use in puzzling jaundice. Watson [4] stated he preferred a small laparotomy and cholangiography, since difficulty in needling the gallbladder had been encountered. Royer, Mazure and Kohan [5] reported 86 instances in which they had performed peritoneoscopic cholangiography safely without undue discomfort to the patient.

We have found the method useful and practical and have used it in problem cases in which history, results of physical examination, clinical course, outcome of liver function tests and other types of cholecystography failed to establish a diagnosis.

TECHNIQUE

The patient is prepared for peritoneoscopy. Meals are not withheld. Morphine, 4 to 16 mg., and scopolamine hydrobromide, 0.4 mg., are administered subcutaneously, and 100 mg. of secobarbital (seconal®) sodium is given orally one hour before the procedure. The abdomen is

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This study was from the Department of Internal Medicine, Veterans Administration Hospital, Des Moines, Iowa.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Lee, W. Y.: La Peritoneoscopia, J. Internat. Coll. Surgeons **4**:511-519 (Dec.) 1941; Evaluation of Peritoneoscopy in Intra-Abdominal Diagnosis, Rev. Gastroenterol. **9**:133-141 (March-April) 1942.

2. Hodges, F. J.: The Gastro-Intestinal Tract, Chicago, The Year Book Publishers Inc., 1944, p. 184.

3. Royer, H., and Solari, A. V.: Cholangiography Performed with the Help of Peritoneoscopy, Gastroenterology **8**:586-591 (May) 1947.

4. Watson, C. J.: The Prognosis and Treatment of Hepatic Insufficiency, Ann. Int. Med. **31**:405-423 (Sept.) 1949.

5. Royer, M.; Mazure, P., and Kohan, S.: Biliary Dyskinesia Studied by Means of the "Peritoneoscopic Cholangiography," Gastroenterology **16**:83-90 (Sept.) 1950.

shaved and cleansed, and a small area down to and including the parietal peritoneum is infiltrated with 1 per cent procaine (novocain®) hydrochloride solution. The peritoneoscope is introduced, usually about 1 inch (2.5 cm.) to the left of and below the umbilicus. The gallbladder is readily visualized and identified by its anatomic position, cystic structure and blue-green color. The anterior abdominal wall, or lower part of the chest, is indented by external palpation to localize the site of introduction of the needle. After infiltration a stab wound is made through the skin overlying the gallbladder, and an ordinary 6 inch (15.2 cm.) no. 20 needle is inserted. This is readily guided to the body or fundus of gallbladder under direct vision. With a brisk stroke it is ordinarily possible to enter the gallbladder cavity at once, though occasionally further manipulation is required.

Variable quantities of bile are then aspirated, and 15 to 40 cc. of iodopyracet concentrated solution (70 per cent diodrast® solution), containing 5 cc. of 1 per cent procaine hydrochloride solution, is injected slowly, care being taken to watch for spillage of either bile or iodopyracet solution into the peritoneal cavity. We have used a small amount of iodopyracet concentrated solution (10 cc.) and 30 to 40 cc. of air for double contrast. After removal of the peritoneoscope and needle, roentgenograms are taken immediately and at five and 15 minutes. A fatty meal is then administered, and films are taken 15 and 30 minutes later.

REACTIONS

Occasionally a patient will experience pain with rigidity in the right upper abdominal quadrant for a few hours following the examination. This is observed as frequently in peritoneoscopy when cholangiography is not done and is apparently due to parietal peritoneal irritation caused by traumatizing the peritoneum with the tip of the instrument.

In two cases we have inadvertently injected dye into the gallbladder wall. This has produced a chemical cholecystitis, with severe, constant pain in the right upper quadrant and vomiting for several hours. In both cases these symptoms subsided with conservative management. In one of these cases cholecystectomy was performed two weeks later. The wall of the gallbladder was gray-yellow. Microscopic examination showed chronic cholecystitis. This complication can be avoided by assuring a free flow of bile through the aspirating needle prior to and during injection of the dye.

No more than a few drops of bile have been observed escaping through the needle hole. Usually none escapes. Bile peritonitis or fistula has not been encountered.

Ambulation is immediate, and no significant reaction has been observed.

COMMENT

Cases in which it is impossible to distinguish between primary hepatocellular damage and secondary hepatic damage due to common duct stone are frequently encountered. For the patient's welfare it is extremely important to decide which condition exists. Patients with far advanced hepatic disease do not tolerate major operative procedures well, and exploration of the biliary system may be sufficient to produce hepatic coma from which the patient will not recover. Peritoneoscopic cholangiography is a relatively harmless procedure indicated only in those cases in which diagnosis by other means is impossible.

We have seen a number of cases in which the history and results of liver function tests were compatible with infectious hepatitis, but over the period of

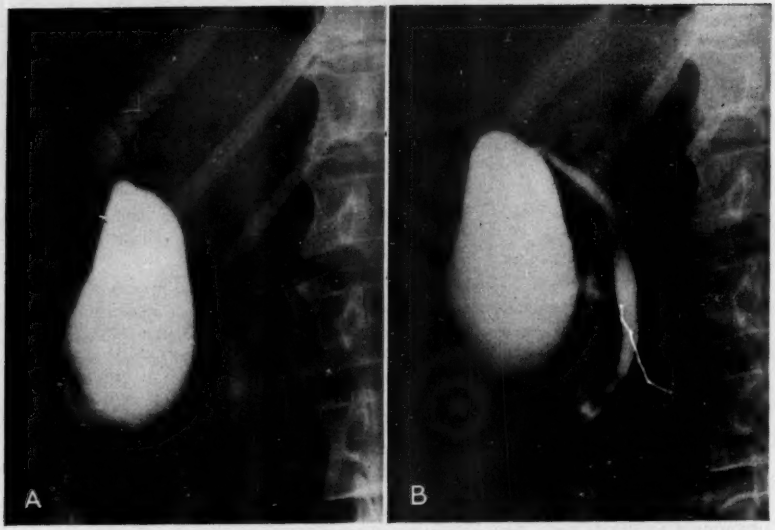

Fig. 1.—*A*, cholangiogram of patient M. S. taken five minutes after injection of 30 cc. of iodopyracet concentrated solution into the gallbladder. The end of the common duct is filled, but no dye has entered the duodenum. Slight leakage of iodopyracet solution from the puncture site is evident. *B*, cholangiogram of patient 15 minutes after injection. The cystic and common ducts are now outlined, and beginning duodenal filling is apparent. This patient was a 60 year old woman, thought clinically to have common duct stone.

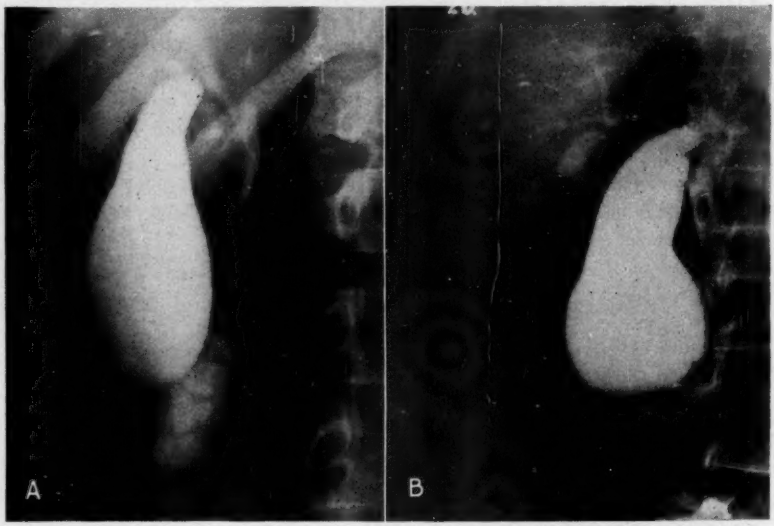

Fig. 2.—*A*, cholangiogram of patient R. R. 15 minutes following injection of 25 cc. of iodopyracet concentrated solution directly into gallbladder. There is no spillage. The cystic and common ducts are outlined, and there is slight reflux into the hepatic duct. Duodenal filling is evident. *B*, shows the gallbladder of patient C. L. outlined on the five minute film. There is considerable retrograde filling of hepatic radicles and no filling of the cystic or common duct. Later films showed these ducts and the emptying time of the gallbladder to be normal.

hospital treatment the serum alkaline phosphatase steadily increased to values of 20 and 30 Bodansky units. To rule out the possibility of ductal stone, we have performed cholangiography and have been successful in demonstrating normal ducts in these cases. Conversely, a stone impacted in the common duct produces progressive hepatic damage, manifested first as a disturbance of cholangiolar function. If other means of diagnosis fail, nonopaque stones in the ductal system can be demonstrated by peritoneoscopic cholangiography. Immediate surgical intervention minimizes the possibility of further diffuse hepatic damage.

Patients with far advanced hepatic disease are extremely sensitive to small doses of opiates and barbiturates. Morphine premedication is avoided when possible.

By peritoneoscopic cholangiography the gallbladder, cystic duct and common duct can be visualized in their entirety (fig. 1). The cystic duct is of variable length and 1.5 to 4 mm. in diameter. The common duct, also of variable length,

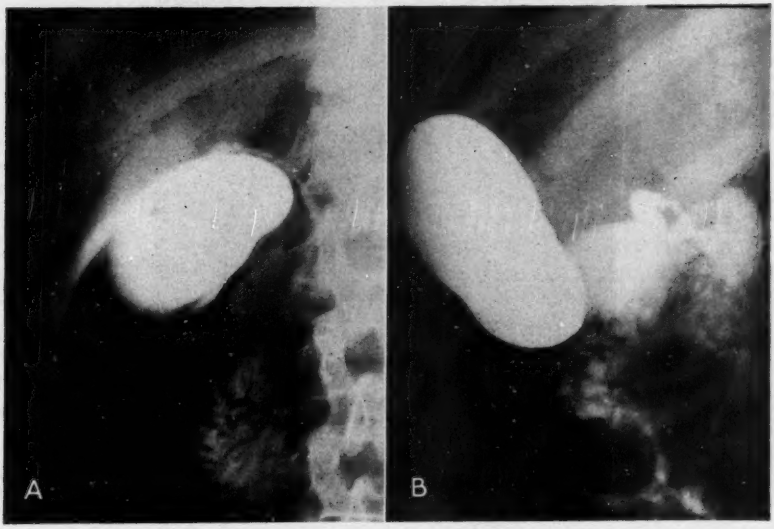

Fig. 3.—*A* (patient L. H.), film taken 30 minutes after injection of 20 cc. of iodopyracet concentrated solution. There is some spillage into the lateral gutter. The cystic and common ducts are outlined down to the duodenum, and considerable duodenal filling is evident. This patient was a 55 year old man who entered the hospital with a history of colicky pain in the right upper quadrant relieved by administration of morphine, followed in 72 hours by progressive icterus. Clinical diagnosis was common duct stone, though the results of liver function tests were more compatible with the diagnosis of hepatitis. Direct cholangiography was performed to rule out duct stone. Roentgenographically the gallbladder and duct system were normal, and the patient's subsequent course was that of chronic infectious hepatitis. *B*, a roentgenogram of the gallbladder area of patient E. T. following injection of 35 cc. of iodopyracet concentrated solution. The gallbladder appears twisted on itself, but the cystic and common ducts are normal, and there is considerable duodenal filling, indicating normal emptying time. This patient was a 35 year old white man who entered the hospital with the history of chronic infectious hepatitis. Results of liver function tests were confirmatory. During treatment his condition did not improve, and the alkaline phosphatase steadily increased to values above 30 Bodansky units. Intravenous cholecystogram showed no filling. Common duct stone was ruled out by direct cholangiography.

is 2 to 8 mm. in diameter, and the distal 1 cm. (intrapancreatic portion) is ordinarily tapered at its junction with the duodenum. Emptying time is variable. On occasion there is considerable intestinal filling on the five minute roentgenogram, while in other cases filling of the common duct is delayed for as long as an hour, even when there is no retrograde filling of the hepatic ducts. According to Royer,[5] filling of the hepatic ducts is abnormal and is seen only in cases of biliary dyskinesia. We have seen filling of the hepatic ducts in four instances, and in none of these was there a clinical history compatible with dyskinesia (figs. 2 and 3). Nonopaque stones in the gallbladder or ducts are evident as shadows of negative density when

Fig. 4.—Cholecystogram of patient E. S. immediately after injection of 15 cc. of iodopyracet concentrated solution. The gallbladder is small. The cystic duct and common duct are greatly dilated and tortuous. There is a shadow of negative density just above the ampulla, and another rounded shadow of negative density appears in the proximal cystic duct. This patient was middle aged and gave the history of dull pain in the right upper quadrant for several weeks. Results of the liver function tests were abnormal. There was a difference of opinion clinically whether the hepatic dysfunction was primary or secondary to ductal stone. The stones were removed surgically, and the patient's postoperative course has been uneventful.

the ducts are filled with opaque medium (figs. 4 and 5). Dilatation of the cystic duct above 5 mm. and of the common duct above 8 mm. is indicative of obstruction.[9] The gallbladder is visualized in nearly all peritoneoscopic examinations. Needling of this organ is not difficult. The contrast obtained is sufficient for fluoroscopic examination and spot filming.

Excellent contrast is obtained when 15 to 40 cc. of iodopyracet concentrated solution is used. Ordinarily, the normal gallbladder does not empty all traces of dye for several hours.

The method is valuable when oral and intravenous cholecystography fails. It is the only means of visualizing the ducts roentgenographically, except for cholangiography performed during laparotomy.

Fig. 5.—Cholecystogram of patient E. F. made after the injection of 10 cc. of iodopyracet concentrated solution and 40 cc. of air into the gallbladder. A large solitary stone is apparent within the gallbladder cavity as a shadow of negative density. This patient had had repeated attacks of cholecystitis, and oral and intravenous cholecystography failed to opacify the gallbladder. Cholecystectomy was performed, and a large solitary stone was present.

SUMMARY

Peritoneoscopic cholangiography is a diagnostic method available in cases of biliary tract disease which defy the usual means of diagnosis.

Excellent visualization of the gallbladder, cystic duct and common duct is obtained.

Bile peritonitis or other complications have not been observed.

With the use of this method, patients with severe hepatic disease may be spared an operative procedure which will provoke irreversible hepatic insufficiency.

The patient with common duct stone may be spared the delay which leads to severe hepatic damage and suppurative cholangitis.

Dow Air Force Base, Bangor, Maine (Major Keil).

Forbes Air Force Base, Topeka, Kan. (Major Landis).

Miss Elaine Strubbe gave technical assistance.

LATE EFFECTS OF THORIUM DIOXIDE IN MAN

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THE USE of thorium dioxide in man has been controversial since its introduction in 1930.[1] In the form of a colloidal suspension, thorium dioxide is a radiopaque diagnostic agent of greatest usefulness in visualizing the liver and spleen. Numerous observers have shown that this particulate material is taken up by the reticuloendothelial system after intravenous injection.[2] The bulk of it is thus concentrated in the liver and spleen, which are then readily visible roentgenographically. In many patients it has been possible to demonstrate such lesions as liver abscesses and tumors without recourse to surgical measures.[3] In this technique of hepatosplenography thorium dioxide is a unique agent.

Some observers have recognized potential dangers in the use of thorium dioxide, in view of its prolonged radioactivity and apparently permanent domicile in the body.[4] In experimental animals it has been possible to produce malignant tumors with the use of thorium dioxide.[5] Other studies have shown damage to liver and spleen, blockade of the reticuloendothelial system and failure of the animals to

This study was supported in part by a grant from the John and Mary R. Markle Foundation.

From the Departments of Medicine, Radiology and Pathology, Duke University School of Medicine.

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excrete the substance.[2b, c] Most of these effects followed larger doses than are employed in patients. Some early untoward effects have been reported in man, especially after angiography and tissue infiltration.[6] However, the preponderance of evidence favors the conclusion that no significant ill effect of thorium dioxide can be found for at least a few years after its intravenous administration.[7] Few data are available from longer term observations. One patient died of sarcoma of the liver 12 years after the use of thorium dioxide.[8] Individual cases of aplastic anemia[9] and of fibrosis of the liver and spleen[10] have been reported to occur five or more years after the administration of this substance. The evidence to incriminate thorium dioxide in the pathogenesis of these conditions is suggestive but inconclusive. The purpose of this paper is to report a study on three patients in whom thorium dioxide has been present for many years, and who have been evaluated for observable late effects of this substance.

METHOD OF STUDY

Three patients who had received thorium dioxide sol 17, 16 and 13 years previously were available for hospital study. The plan of the study was to evaluate these patients for any evidences of complications which might accrue from the presence of thorium dioxide. In addition to careful history taking, physical examination and usual laboratory studies, each patient had an abdominal roentgenogram and measurement of gamma radiation over the liver and spleen. In view of the known localization of thorium dioxide in the liver, spleen and bone marrow, particular study of these organs was made. A battery of tests of liver function was performed, as well as needle biopsy of the liver.

REPORT OF CASES

CASE 1.—In September 1933 R. H. C. (unit 5604), a 24 year old mechanic, presented symptoms suggesting liver abscess. Seventy-five cubic centimeters of thorotrast® (a colloidal suspension of thorium dioxide) given intravenously demonstrated a single round rarefaction in the liver. This proved to be an abscess, which was drained through a stab incision. No organisms were found, and the process was thought to be amebic. Healing followed a course of treatment with emetine hydrochloride.

On sporadic clinic visits the patient continued to complain of vague pain in the right upper abdominal quadrant. He admitted consuming 1 pint (473 cc.) of whisky daily, as well as eight bottles of beer, and stated that his eating habits were irregular. In 1939 hospital study failed to reveal an organic basis for his pain.

The patient returned to the hospital for evaluation of the late effects of thorotrast® in April 1950, 17 years after its administration. At that time he had no complaints, other than intermittent cough productive of small amounts of mucoid sputum. He had continued to consume alcohol

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9. Spier, J.; Cluff, L. E., and Urry, W. D.: Aplastic Anemia Following Administration of Thorotrast, J. Lab. & Clin. Med. **32**:147, 1947.

10. (*a*) Jonsell, J. E., and Lindgren, G. H.: Case of Hepatosplenography with Thorotrast: Results of Autopsy 10 Years Later, Radiol. Clin. **13**:201, 1944. (*b*) Jacobson, L. E., and Rosenbaum, D.: Postmortem Findings and Radio-Activity Determinations 5 Years After Injection of Thorotrast, Radiology **31**:601, 1938.

to the same degree as previously but stated that he had eaten a good diet. There had been no jaundice, weight loss, fever or digestive complaints.

Examination revealed the temperature to be 37 C. (98.6 F.), the pulse rate 100, respirations 20 and blood pressure 130/80. His general appearance was that of a well nourished, tremulous man, with no icterus or spider angiomas. The head and neck were normal. The chest showed increase in the anteroposterior diameter and diffusely scattered rales. The heart was normal. The liver edge extended 2 cm. below the right costal margin and was smooth and nontender. The spleen was not felt, and there were no signs of ascites. The rectal and neurological examinations disclosed no abnormalities.

Laboratory examinations revealed 12.9 Gm. of hemoglobin per 100 cc., an erythrocyte count of 4,200,000 and a white blood cell count of 10,000 per cubic millimeter, with a normal differential count. Urinalysis disclosed nothing unusual. The two hour urinary urobilinogen excretion was 0.4 Ehrlich unit. The stool contained no blood, ova or parasites. The sedimentation rate was 12 mm. per hour (Wintrobe). Serum bilirubin measured 0.85 mg., phosphorus 3.4 mg. and total protein 7.3 Gm., with 3.6 Gm. of albumin and 3.7 Gm. of globulin, per 100 cc. Alkaline phosphatase was 2.4 Bodansky units and thymol turbidity 2.0 units, with 1 + flocculation. Vitamin A measured 38 micrograms per 100 cc. At 45 minutes there was a trace of sulfobromophthalein (bromsulphalein®) sodium retention. Bleeding, clotting and prothrombin times were normal.

Measurement of gamma radiation over the liver and spleen with the Geiger-Müller counter demonstrated definite but slight increase over the background count. Abdominal roentgenograms showed normal-sized liver and spleen, each of which presented a diffusely speckled radiopacity but no localized change. Bone marrow study showed normal cellularity and differential count. Liver biopsy was performed with the Vim-Silverman needle. The specimen showed a mild fibrosis about the portal fields, with some distortion of the liver architecture (fig. 1 *A*). There were irregularly scattered foci of fatty infiltration, but no other parenchymal abnormalities were seen. Small quantities of moderately refractile brownish granular material morphologically identical to thorium dioxide were concentrated in the connective tissue of scattered portal fields, sometimes observed within macrophages and at other times lying loose amidst the tissues. In a few scattered Kupffer cells the same material was seen. There was no apparent inflammatory reaction or necrosis.

Comment.—In view of the history of alcoholism and the observation of fatty change and portal fibrosis within this liver, it would seem reasonable that the hepatic process represented mild cirrhosis of the Laennec type. The presence of thorium dioxide produced no morphologically visible reaction other than its phagocytosis. It bore no uniform relationship to the fibrosis present. It is interesting that in livers from which biopsy specimens were removed soon after thorium dioxide was given the material was observed to be diffusely scattered in the Kupffer cells, as well as in the numerous macrophages which are seen normally in portal fields. After 17 years, most of the material in this case was concentrated in the connective tissue of the portal fields.

Case 2.—A 46 year old housewife, L. S. (unit 42533), was admitted Aug. 28, 1934 because of pain along the right anterior costal margin of three weeks' duration. This had been accompanied with chills, fever, vomiting and transitory jaundice. Consolidation at the base of the right lung and tenderness in the right upper abdominal quadrant were noted. After initial studies she was given 75 cc. of thorotrast® to rule out the presence of a liver abscess. The liver showed no enlargement or radiolucent areas. Shortly thereafter an abscess developed in the consolidated lung, followed by recovery.

The patient gave a past history of recurrent bouts of abdominal pain, fever and jaundice suggesting choledocholithiasis, following a cholecystectomy 10 years previously.

There was then no contact with the patient until she was called back for study of the effects of thorotrast,® April 17, 1950, 16 years after its administration. In the interval the patient had had intermittent epigastric and right upper quadrant pain occasionally relieved by food. In 1946 she apparently had an episode of hematemesis and melena. On the current admission, her general health was good and she had no complaints. Her dietary history suggested an entirely adequate intake of protein and no alcoholism at any time.

Results of Examination.—The patient was obese and apparently healthy, with normal temperature and pulse rate and blood pressure of 185/98. The retinal arterioles showed moderate hypertensive changes. The heart and lungs were normal. A rounded, slightly tender liver edge was

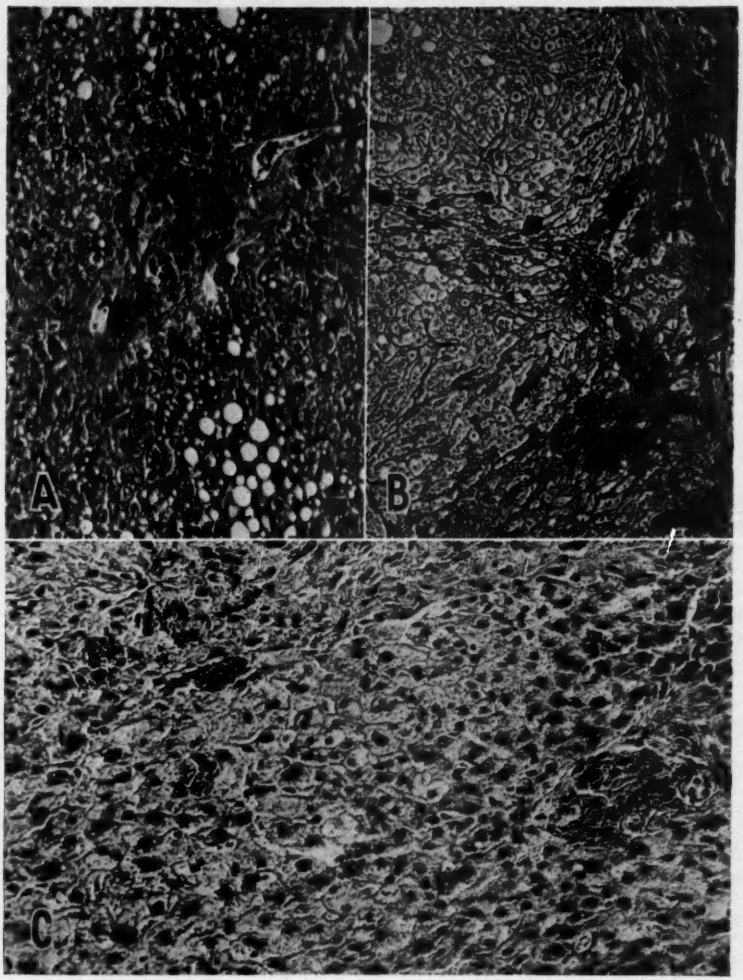

Fig. 1.—*A* (case 1), liver biopsy specimen from an alcoholic patient 17 years after thorium dioxide administration, showing mild fibrosis about the portal field and moderate fatty infiltration. Collections of thorium granules both in phagocytes and lying free are seen as the dark material in the portal field. High power; hematoxylin and eosin stain. *B* (case 2), liver biopsy specimen 16 years after thorium dioxide administration, showing moderate fatty metamorphosis and architectural distortion produced by the irregular portal fibrosis. Some collections of thorium granules are apparently lying free, but most are within cells in portal fields. Some clusters of thorium material are not surrounded by fibrosis. Low power; Wilder stain for reticulin fibers. *C* (case 3), liver biopsy specimen 13 years after the administration of thorium dioxide, showing normal parenchyma and architectural pattern. Clusters of cells containing dark, slightly refractile thorium particles are seen in the portal field (lower part), with no surrounding reaction, and in Kupffer cells (upper left). High power; hematoxylin and eosin stain.

felt 5 cm. beneath the right costal margin at the midclavicular line. Results of the general physical examination were otherwise normal.

The results of the laboratory examinations were as follows: The hemoglobin concentration was 14 Gm. per 100 cc. Red blood cells numbered 5,200,000 and white blood cells 6,050 per cubic millimeter, with a normal differential count. Urinalysis gave essentially normal results. The two hour urinary urobilinogen excretion was 1.0 Ehrlich unit. The fasting blood sugar level was 88 mg., nonprotein nitrogen 32 mg., serum bilirubin 0.4 mg., total protein 6.7 Gm. (3.9 Gm. of albumin and 2.8 Gm. of globulin), phosphorus 3.7 mg. and cholesterol 235 mg., per 100 cc. The thymol turbidity test showed 0 units of turbidity and no flocculation. Alkaline phosphatase was 5.8 Bodansky units. Bleeding, clotting and prothrombin times were normal. Vitamin A measured 55 and carotene 217 micrograms per 100 cc. The stool did not contain occult blood. Bone marrow study showed normal differential and total counts.

Chest fluoroscopy revealed nothing unusual. A gastrointestinal roentgenographic series showed a diverticulum of the second portion of the duodenum. There was no evidence of esophageal varices. An abdominal roentgenogram disclosed increased density of the liver and the spleen

Fig. 2 (case 2).—Abdominal roentgenogram taken 16 years after the administration of thorium dioxide, showing the persistent opacity of the liver and spleen. The densities below the liver to the right of the spine are the lymph nodes at the porta hepatis.

and several discrete densities below the midportion of the liver (fig. 2). There was slight but measurable increase in radiation over the liver as compared with the background count, with the use of the Geiger-Müller counter.

A needle biopsy specimen of the liver showed an irregular portal fibrosis which altered the general liver architecture (fig. 1 *B*). The liver cells displayed moderately severe fatty metamorphosis. In some portal fields a chronic mononuclear reaction of mild degree was seen, while in others there was no inflammatory reaction. In certain portal fields a moderately refractile tannish granular material, morphologically identical to thorium dioxide, was seen usually within phagocytes but sometimes apparently lying free. This material appeared both in portal fields which showed fibrosis and in those in which there was no increase in fibrous tissue. Sometimes the foreign material was seen in a group of Kupffer cells in the sinusoids, without surrounding fibrosis. Throughout the liver there was moderate morphological variability of liver cell nuclei. There was no increase in this variability in liver cells immediately surrounding large deposits of thorium dioxide.

Comment.—This patient afforded the opportunity for study of the effects of thorium dioxide administered 16 years previously. On her general health and hemopoietic function there was no untoward effect. The interpretation of the fibrosis, which was the only important hepatic lesion in this biopsy specimen, was complicated by the variety of possible etiological factors. The pattern of fibrosis was that of Laennec's cirrhosis rather than that of biliary cirrhosis. The fatty infiltration, furthermore, was consistent with Laennec's cirrhosis, despite the history of adequate diet. The presence of thorium dioxide granules in portal fields is to be expected months or years following the intravenous administration of thorotrast.® Therefore, one cannot attribute portal fibrosis to the mere presence of thorium dioxide at this site, since this may be a pure coincidence. In this biopsy specimen the substance was present in normal portal fields, as well as in those with fibrosis. That thorium dioxide was the etiological agent for the hepatic abnormalities demonstrated is questionable.

CASE 3.—In July 1936 a 22 year old white carpenter, H. E. (unit 69734), presented the diagnostic problem of a tender mass in the right upper abdominal quadrant, chills, fever and moderate weight loss developing over a period of four months. In order to determine whether or not the mass was caused by a liver abscess, 75 cc. of thorotrast® was given intravenously. The abdominal roentgenogram then showed a normal-sized liver displaced upward by a mass which proved to be a huge pyonephrosis sac. He recovered after nephrectomy was performed.

For 13 years the patient was not seen at the hospital. Then on Nov. 4, 1949 he returned, complaining of excruciating abdominal pain of two hours' duration. In the previous 10 years he had recurrent episodes of epigastric distress relieved by antacids and otherwise typical of peptic ulcer. No melena, vomiting or other complication had occurred. While at work, he was suddenly seized with cramping epigastric pain and was brought to the hospital.

Examination showed a well nourished, acutely ill man with a temperature of 37.6 C. (99.7 F.), a pulse rate of 100 and a blood pressure reading of 102/70. No significant abnormalities were observed on the general physical examination, except for diffuse abdominal tenderness and rigidity.

An upright abdominal roentgenogram disclosed no free air beneath the diaphragm. The liver and spleen showed diffuse finely speckled opacification. The hemoglobin concentration was 14.5 Gm. per 100 cc. White blood cells numbered 17,000. Urinalysis revealed nothing abnormal. Nonprotein nitrogen measured 46 mg. per 100 cc. The carbon dioxide-combining power was 64 volumes per cent, and chlorides were 100.5 milliequivalents per liter.

The clinical impression was perforated peptic ulcer. At operation a perforated duodenal ulcer was found and closed, following which the patient made an uneventful recovery. He was then studied to ascertain whether there were any effects from the thorium dioxide given 13 years previously. The laboratory examinations revealed 15 Gm. of hemoglobin per 100 cc., 4,400,000 erythrocytes per cubic millimeter, hematocrit of 39 per cent and a white blood cell count of 8,450, with a normal differential count. Liver function tests gave the following results: serum bilirubin, 0.7 mg. per 100 cc. (indirect); thymol turbidity, 1.5 units, with no flocculation; alkaline phosphatase, 2.0 Bodansky units; total protein, 6.7 Gm., with 3.0 Gm. of albumin and 3.7 Gm. of globulin, per 100 cc.; vitamin A, 50 micrograms per 100 cc.; two hour urinary urobilinogen excretion, 0.76 Ehrlich unit; sulfobromophthalein sodium retention, 7 per cent at 30 minutes and a trace at 40 minutes; phosphorus, 3.1 mg. per 100 cc. Bleeding, clotting and prothrombin times were normal.

Measurement of radioactivity over the liver and spleen by the Geiger-Müller counter showed counts 80 per cent greater than the background count. Bone marrow aspiration revealed normal cellularity. A differential count showed slight myeloid immaturity, compatible with the peritoneal reaction. In the marrow smear an occasional reticulum cell containing refractile tan granules was encountered.

Needle biopsy of the liver was performed. The architectural pattern of the liver showed no disturbance, but the connective tissue in the portal fields was somewhat prominent (fig. 1*C*). The parenchyma was normal. In the portal fields there were isolated and clustered histiocytes, which were filled with greenish tan granular material identical to thorium dioxide. There was no noticeable reaction in the liver cells adjacent to this foreign material. The sinusoids showed no inflammatory reaction or other abnormality.

Comment.—Thirteen years after 75 cc. of thorotrast® was given intravenously to this patient there was measurable radioactivity over the liver and spleen. These organs showed a diffuse

particulate density on the abdominal roentgenogram. A biopsy specimen of the liver revealed collections of granular foreign bodies in histiocytes in portal fields. This distribution of radiopaque substance is the basis for the roentgenologic appearance of the liver. No morphological evidence of reaction to the thorotrast® was seen. Liver function tests all gave normal results except for slight elevation of serum globulin. The peripheral blood and bone marrow were essentially normal. In this patient, despite the presence of radioactive thorium dioxide for 13 years, no demonstrable ill effects were observed.

COMMENT

At the outset it is realized that no valid conclusions regarding the over-all potential dangers of thorium dioxide, or of any other radioactive agent, can be reached by the clinical evaluation of a few cases. The observations reported are confined to a few of the many patients who have received this material. Long term follow-up study of patients in whom hepatosplenography was performed is necessarily limited. Most of the patients initially had an underlying malignant disease, and this technique was used to demonstrate possible hepatic metastases. Naturally, most of these patients would have died within a relatively short time. Any patient who may have died from a complication of thorium dioxide administration through the years might be unknown to those who administered it originally. The ultimate status of the hazards involved in the clinical use of this substance will rest on long range follow-up observation of patients.

The fact that thorium dioxide is largely retained once administered intravenously is incontrovertible. Excretion studies have indicated minute loss in the urine and feces.[11] The finding of thorium-filled phagocytes in pulmonary capillaries and in tracheobronchial mucus has suggested that some of the material originally phagocytosed in the liver might find its way into the circulation to the lungs, and thence be excreted.[2a] Nevertheless, the total excretion of thorium dioxide seems to be quite small, as the radioactivity measurement of incinerated organs up to a few years after intravenous use of thorium dioxide accounts for the bulk of the material.[12] In the living subject it is not possible to determine accurately the quantity of thorium dioxide present by measurement of gamma radiation.[11] Thus, in this group of patients the Geiger-Müller counter was used only to detect the presence of radioactive material in the liver and spleen; very slight radiation was demonstrated.

Thorium preparations continuously decay to other radioactive substances, with the large proportion of potentially hazardous energy emitted as alpha radiation. It has been calculated that the usual dose of thorotrast® has an alpha ray activity equivalent to that of 1.5 micrograms of radium, an amount known to produce toxic effects.[13]

With the apparently permanent retention of thorium dioxide, and its indeterminately prolonged radioactivity, the possibility of eventual harmful effects has been recognized.

In 1932 the Council on Pharmacy and Chemistry of the American Medical Association declined to accept thorotrast® in view of the inherent dangers in its

11. Stenstrom, W.: Elimination of Radio-Active Elements by Patients and Rabbits After Injection of Thorotrast, Radiology **37**:698, 1941.

12. Taft.[4a] Jacobson and Rosenbaum.[10b] Reeves, R. J., and Morgan, J. E.: Retention of Thorotrast by Reticuloendothelial System, Radiology **29**:612, 1937.

13. Taft.[4a] Potential Hazards of the Diagnostic Use of Thorium Dioxide, editorial, J. A. M. A. **108**:1656 (May 8) 1937.

use.[4b] Some clinicians have employed it freely, while others have restricted its use to either persons of the older age group or patients in whom hepatosplenography is a vital and necessary procedure.

The roentgen appearance of the liver and spleen soon after the administration of thorium dioxide changes with the passage of months or years. Some diminution in the opacity of the liver may occur, but the liver and spleen are still strikingly demonstrated as long as 17 years later. Unfortunately, the original roentgenograms of our patients were not available for comparison. Initially there is a diffuse, homogeneous opacity, while later this assumes a finely speckled appearance, as reported by Rigler and associates.[14] The probable morphological basis for this roentgen change in the liver is found in the distribution of the thorium dioxide. Soon after its administration granules of thorium dioxide are seen diffusely scattered in the Kupffer cells of hepatic sinusoids. The liver tissue examined after a number of years shows clumping together of thorium dioxide in portal fields, and this uneven distribution probably accounts for mottled shadows. Another roentgen feature is the appearance of discrete dense shadows in the region of the porta hepatis. This has been shown to be due to an accumulation of thorium dioxide in the lymph nodes draining the liver.[15]

A relatively radiolucent area in the liver following hepatosplenography indicates the presence of a tumor, cyst or abscess, which displaces the phagocytic elements and consequently displaces the radiopaque material. Such areas may be of sufficient size to be grossly visible on the films. The absence of areas of relative rarefaction in the patients studied suggests that no grossly visible tumors have developed. Certainly this does not rule out the development of neoplasm in the liver, just as the minute, random specimen of liver tissue removed for biopsy cannot rule it out.

The one striking feature of host reaction to the presence of thorium dioxide in the liver is phagocytosis. In these liver biopsy specimens the greatest part of the thorium dioxide is contained within cells of the histiocytic type. However, collections of granules are also seen lying free in the tissues. Other than this one feature, no evidence of reaction was observed with any consistency. No inflammatory, necrotizing or neoplastic reaction was seen in relation to the foreign material. In the two cases in which definite fibrosis occurred, there was no direct evidence that the thorium dioxide was responsible, in view of the fact that thorium was seen both in juxtaposition to areas of fibrosis and also in contact with morphologically normal cells, and that fibrosis was present both with and without adjacent thorium granules. Further, the characteristics of the cirrhotic process differed in no respect from those of the usual type of Laennec's cirrhosis. At the same time, the evidence on which one can base any conclusions is limited here by the single, minute specimen of liver tissue which may or may not be representative of the general hepatic process. The tissue specimen is 1 mm. in diameter and usually 2 cm. in length, precluding an entirely adequate evaluation of the general architectural pattern.

Despite the equivocal evidence of the pathogenetic role of thorium dioxide, the fact remains that two of these three cases showed morphological evidence of cirrhosis. In other isolated studies of patients several years after thorium dioxide

14. Rigler, L. G.; Koucky, R., and Abraham, A. L.: The Effects of Thorium Dioxide Sol on the Human Liver, Radiology **25**:521, 1935.

15. Jacobson and Rosenbaum.[10b] Rigler and others.[14]

administration, a rather surprising occurrence of cirrhosis is reported. Jonsell and Lindgren [10a] reported a case of such findings at autopsy, and Jacobson and Rosenbaum [10b] reported another, 10 and five years respectively, after the use of thorium dioxides. In both of these cases death was due to an incidental cause. In the extensive experience of Yater and of Rigler cirrhosis has not occurred, though their published cases are of shorter duration of observation. Thus, whether or not parenchymal hepatic damage occurs and is followed by fibrosis remains a moot point.

The survey of the results of liver function tests performed on the three patients of this report disclosed no evidence of significant abnormality. It is, of course, well known that liver function tests are crude, and the information they furnish is of limited value. Morphological changes in the liver, whether localized or diffuse, may be associated with no significant abnormalities in the currently used laboratory tests.

Study of the peripheral blood and the bone marrow of these patients revealed no evidence of abnormal hemopoiesis. Spier, Cluff and Urry [9] reported on a patient who died of aplastic anemia nine years after the administration of thorium dioxide. They observed cells laden with thorium granules scattered in the bone marrow and attributed the bone marrow depression to the presence of this material. In one of the patients reported here occasional thorium-filled reticulum cells were observed in the bone marrow smear, while other observers have similarly seen retained thorium in the reticuloendothelial elements of marrow. However, none of the reports establishes evidence of diffuse bone marrow depression or significant focal change due to thorium dioxide. Thus, no significant late effect on hemopoiesis has been conclusively shown.

SUMMARY

In order to assess the late effects of thorium dioxide three patients were studied, 17, 16 and 13 years, respectively, after its administration. The persistence of thorium dioxide was shown by roentgen opacity of the liver and spleen, the demonstration of gamma radiation over these organs and the presence of material morphologically compatible with thorium dioxide in liver tissue obtained by needle biopsy. No significant effect on hemopoiesis, hepatic function or the general health of the patients was disclosed. Liver biopsy specimens showed clumps of phagocytes containing the granular material largely in portal fields, and two patients had changes of Laennec's cirrhosis. There was no evidence that the thorium dioxide had any pathogenetic relationship to the development of hepatic fibrosis, though this possibility exists. None of the specimens showed inflammatory, degenerative or neoplastic alterations in relation to the thorium dioxide.

CONCLUSIONS

In three cases there is no evidence that thorium dioxide has produced significant impairment of liver function, blood formation or general health over the course of many years. No neoplastic reaction was demonstrated. Liver biopsy specimens showed fibrosis in two of the three cases, though its pathogenetic relation to thorium dioxide is not established.

The potential dangers of using material with protracted radioactivity which is permanently retained in the body are not discredited by this study.

The ultimate evaluation of the safety of thorium dioxide in hepatosplenography awaits further long range studies.

HYPERTENSIVE AND NONHYPERTENSIVE PERIARTERITIS NODOSA

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IN THE compilation from the literature by Harris, Lynch and O'Hare,[1] hypertension was found in two thirds of the reported cases of periarteritis nodosa. In the large single series of 29 cases reported by Ralston and Kvale,[2] there was hypertension in 20, and in five of these cases the condition was considered to be primary hypertension. Elevation of blood pressure is known to develop fairly frequently during the course of periarteritis nodosa. For this reason the hypertension of periarteritis nodosa is usually thought to be secondary in character. Hypertension, often asymptomatic and of unknown origin, occurs with sufficient frequency in the general adult population to account for the occasional chance development of periarteritis nodosa in a person whose blood pressure is already elevated. There is, however, some evidence to suggest that elevation of blood pressure may predispose to the development of periarteritis in certain susceptible persons.

The inflammatory arterial lesions of periarteritis are observed most commonly in the same organs as are the necrotizing arteriolar lesions of hypertension, namely, in those of the splanchnic area. Even when the arterial lesions of periarteritis nodosa are widespread, they still tend to be most numerous and severest in the abdominal viscera. In fulminating cases of severe hypertension the arteriolar lesions often have an inflammatory component, so that the change is sometimes designated "necrotizing arteriolitis." Transition or borderline cases are sometimes encountered that are hard to distinguish from true examples of periarteritis nodosa. Parker and Weiss [3] noted pulmonary arteriolitis in cases of pulmonary hypertension due to mitral stenosis. Lesions of periarteritis nodosa limited to the lungs have been observed in a case of pulmonary hypertension due to cardiac malformation.[4] Rats with spontaneous chronic renal disease and cardiac hypertrophy presumably due to hypertension often

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1. Harris, A. W.; Lynch, G. W., and O'Hare, J. P.: Periarteritis Nodosa, Arch. Int. Med. **63**:1163-1182 (June) 1939.

2. Ralston, D. E., and Kvale, W. F.: The Renal Lesion of Periarteritis Nodosa, Proc. Staff Meet., Mayo Clin. **24**:18-27, 1949.

3. Parker, F., Jr., and Weiss, S.: The Nature and Significance of the Structural Changes in the Lungs in Mitral Stenosis, Am. J. Path. **12**:573-598, 1936.

4. Old, J. W., and Russell, W. D.: Necrotizing Pulmonary Arteritis Occurring with Congenital Heart Disease (Eisenmenger Complex): Report of Case with Necropsy, Am. J. Path. **26**:789-806, 1950.

display arterial lesions that are indistinguishable from those of human periarteritis.[5] Experimental renal hypertension in rats [6] and in other animals [7] is frequently followed by the development of similar lesions. All these observations indicate that the frequent association of hypertension with periarteritis may be more than coincidental.

Hypersensitivity has been more firmly established as a major etiological factor in periarteritis nodosa. The evidence on which this view is based has been presented by Rich.[8] It would be remarkable if two such unrelated conditions as hypertension and hypersensitivity should favor the development of the same inflammatory process in the arterial system. The present study was undertaken in order to determine (1) whether preexisting hypertension is, on occasion, a factor in the subsequent appearance of periarteritis nodosa and (2) whether any consistent differences can be found in hypertensive and nonhypertensive examples of this disease.

MATERIALS AND METHODS

This analysis is based on a study of 94 cases of periarteritis nodosa. Necropsy observations on 28 of these were made at Bellevue Hospital in the period 1930 to 1950. The remaining 66 cases were ones collected from the literature,[9] in which adequate clinical and pathological data

5. Wilens, S. L., and Sproul, E. E.: Spontaneous Cardiovascular Disease in the Rat: II. Lesions of the Vascular System, Am. J. Path. **14**:201-216, 1938.

6. Wilson, C., and Byrom, F. B.: Vicious Circle in Chronic Bright's Disease: Experimental Evidence from Hypertensive Rat, Quart. J. Med. **10**:65-93, 1941.

7. Smith, C. C.; Zeek, P. M., and McGuire, J.: Periarteritis Nodosa in Experimental Hypertensive Rats and Dogs, Am. J. Path. **20**:721-732, 1944.

8. Rich, A. R.: Hypersensitivity in Disease with Especial Reference to Periarteritis Nodosa, Rheumatic Fever, Disseminated Lupus Erythematosus and Rheumatoid Arthritis, in Harvey Lectures, 1946-1947, Lancaster, Pa., The Science Press Printing Co., 1947, pp. 106-147.

9. Harris and others.[1] Lamb, A. R.: Periarteritis Nodosa: A Clinical and Pathological Review of the Disease, Arch. Int. Med. **14**:481-516 (Oct.) 1914. Ophüls, W.: Periarteritis Acuta Nodosa, ibid. **32**:870-898 (Dec.) 1923. Singer, H. A.: Periarteritis Nodosa with Special Reference to the Acute Abdominal Manifestations: Report of 2 Cases, ibid. **39**:865-889 (June) 1927. Strong, G. F.: Periarteritis Nodosa, with Report of a Case, Canad. M. A. J. **19**:534-546, 1928. Bennett, G. A., and Levine, S. A.: Two Cases of Periarteritis Nodosa: One with Unusual Manifestations (Meningeal Form), Am. J. M. Sc. **177**:853-859, 1929. Kountz, W. B.: Periarteritis Nodosa: Report of a Case, Arch. Path. **10**:55-65 (July) 1930. Arkin, A.: Clinical and Pathological Study of Periarteritis Nodosa, Am. J. Path. **6**:401-426, 1930. Curtis, A. C., and Coffey, R. M.: Periarteritis Nodosa: A Brief Review of the Literature and Report of One Case, Ann. Int. Med. **7**:1345-1358, 1934. Krahulik, L.; Rosenthal, M., and Loughlin, E. H.: Periarteritis Nodosa (Necrotizing Panarteritis) in Childhood with Meningeal Involvement, Am. J. M. Sc. **190**:309-317, 1935. Middleton, W. S., and McCarter, J. C.: The Diagnosis of Periarteritis, ibid. **190**:291-308, 1935. Wever, G. K., and Perry, I. H.: Periarteritis Nodosa: Report of Case with Fatal Perirenal Hemorrhage, J.A.M.A. **104**:1390-1395 (April 20) 1935. Bernstein, A.: Periarteritis Nodosa Without Peripheral Nodules Diagnosed Antemortem, Am. J. M. Sc. **190**:317-325, 1935. Spiegel, R.: Clinical Aspects of Periarteritis Nodosa, Arch. Int. Med. **58**:993-1040 (Dec.) 1936. Kernohan, J. W., and Woltman, H. W.: Periarteritis Nodosa, a Clinicopathologic Study with Special Reference to the Nervous System, Arch. Neurol. & Psychiat. **39**:655-686 (April) 1938. Weir, D. R.: Polyarteritis Nodosa: Report of a Case, Am. J. Path. **15**:79-88, 1939. Fitz, R.; Parks, H., and Branch, C. F.: Periarteritis Nodosa: Report of a Case, Arch. Int. Med. **64**:1133-1155 (Dec.) 1939. Blaisdell, E. R., and Porter, J. E.: Healed Stage of Periarteritis Nodosa: Report of a Case, New England J. Med. **224**:1087-1090, 1941. Baker, L. A.: Periarteritis Nodosa, with Report of 2 Cases, Ann. Int. Med. **17**:223-235, 1942. Jones, G. M.: Periarteritis Nodosa, with Case Report, ibid. **16**:920-940, 1942. Finkelstein, W., and Brennan,

were provided. The majority of the reported cases had to be discarded because of insufficient data. In the older reports there is often no mention of blood pressures, differential white blood cell counts or possible allergic manifestations. In the more recent reports detailed descriptions of the distribution of lesions are often omitted.

The 66 cases collected from the literature represent a more heterogeneous group than those from the Bellevue Hospital series. It is obvious that inconstant criteria were sometimes used in the identification of mild, healed or atypical lesions by the various authors. Many of the more recent cases are reported because of unusual features or to emphasize the relation to hypersensitivity.

A history of hay fever, bronchial asthma, skin or other allergic reactions to food or drugs and an unexplained eosinophilia of more than 4 per cent after the onset of periarteritis nodosa were considered to be evidence of hypersensitivity. A blood pressure of 155/95 mm. Hg or over was considered to be evidence of hypertension.

The distribution of arterial lesions was accepted as stated in the necropsy protocols and in the reported cases. This distribution will vary with the number of organs studied histologically and the number of blocks of tissue taken from each organ. It is admitted, therefore, that the number of lesions detected and their distribution as recorded below are probably inaccurate, since it is obvious that not all cases were studied with the same degree of thoroughness.

RESULTS

Incidence of Hypertension in Periarteritis Nodosa.—The 94 cases were subdivided into four groups as follows:

Group I. Preexisting Hypertension: Those cases in which there was a definite history of hypertension dating back four years or more before the onset of evidence of periarteritis.

Group II. Initial Hypertension: Those cases in which hypertension was noted on first examination or was known to have been present only a short time before the onset of periarteritis nodosa.

Group III. Secondary Hypertension: Those cases in which hypertension developed during the course of the disease.

Group IV. No Hypertension: Those cases in which the blood pressure was never significantly elevated.

It is difficult to date the time of onset of periarteritis nodosa in any particular instance, and the disease often runs a protracted course. It was thought, however, that four years of hypertension without any other evidence of the disease would preclude the possibility that elevation of blood pressure was a secondary manifestation. Group II, designated as initial hypertension, is a mixed and artificial one that

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P. J.: Periarteritis Nodosa: Brief Review and Case Report, Connecticut M. J. **7**:104-106, 1943. Solomon, S.; Kasich, M., and Kiven, N.: Periarteritis Nodosa, with Report of 3 Cases Diagnosed During Life, Ann. Int. Med. **21**:638-644, 1944. Webb, A. C.: Periarteritis Nodosa in Pregnancy, Arch. Path. **38**:329-331 (Nov.) 1944. Herbut, P. A., and Price, A. H.: Periarteritis Nodosa Producing Aneurysm of the Renal Artery and Hypertension, ibid. **39**: 274-278 (April) 1945. Logue, R. B., and Mullin, F.: Polyarteritis Nodosa: Report of 11 Cases with Review of Recent Literature, Ann. Int. Med. **24**:11-26, 1946. Lichtenstein, L., and Fox, L. J.: Necrotizing Arterial Lesions Resembling Those of Periarteritis Nodosa and Focal Visceral Necrosis Following Administration of Sulfathiazole: Report of a Case, Am. J. Path. **22**:665-677, 1946. Diaz-Rivera, R. S., and Miller, A. J.: Periarteritis Nodosa: A Clinicopathological Analysis of 7 Cases, Ann. Int. Med. **24**:420-443, 1946. King, B. J.: The Clinical Diagnosis of Periarteritis Nodosa: Report of 4 Cases, ibid. **32**:466-476, 1950. Rose, M. H.; Litmann, D., and Houghton, J.: Polyarteritis Nodosa: A Clinical and Pathological Study and Report of 6 Cases, ibid. **32**:1114-1143, 1950.

consists of those cases in which elevation of blood pressure occurred early in the course of periarteritis but was secondary to it and those in which undetected hypertension had antedated the inflammatory process. There is no accurate way of separating the two categories. The fourth group probably includes some cases in which secondary elevation of blood pressure may have escaped detection, as in some of the case reports only one or two blood pressure readings were recorded.

When the subdivision is made, the following distribution is obtained:

Group	No.	%
I Preexisting hypertension	11	11.7
II Initial hypertension	35	37.2
III Secondary hypertension	17	18.1
IV No hypertension	31	33.0

Whether or not preexisting hypertension plays a role in the subsequent development of periarteritis nodosa, therefore, depends on how many cases of group II should belong in group I and how many properly fall into group III. It is possible that primary hypertension might be found in 11.7% of cases of periarteritis nodosa by chance alone. If, however, the majority of those with initial hypertension actually

TABLE 1.—*Sex and Age Incidence of Hypertensive and Nonhypertensive Periarteritis Nodosa*

	Group I Preexisting Hypertension No.	Group II Initial Hypertension No.	Group III Secondary Hypertension No.	Group IV No Hypertension No.	Total No.
Male	8	31	15	21	75
Female	3	4	2	10	19
Age, Yr.					
0-9	0	0	0	4	4
10-19	0	2	0	3	5
20-29	1	3	6	6	16
30-39	3	10	5	6	24
40-49	5	7	2	5	19
50-59	1	7	3	4	15
60-69	1	6	1	2	10
70-79	0	0	0	1	1

represent cases of preexisting primary hypertension, it is unlikely that the association of the two diseases is fortuitous. It is improbable that in 48.9% of the cases of periarteritis nodosa there would be an accidentally associated primary hypertension.

Approximately one third of all adults over the age of 30 years who are examined at necropsy in Bellevue Hospital have a history of hypertension. In many of these, however, the major disease process is one that is related to or enhanced by high blood pressure. Hypertension is much less common as a coincidental finding in adults over 30 years of age who die of diseases not associated with elevation of blood pressure. For example, only 10 to 15% of those with tuberculosis, cirrhosis of the liver or carcinoma have hypertension as an incidental clinical finding. By analogy one might expect, therefore, that the chance incidence of preexisting hypertension in persons with periarteritis nodosa would be of the same order of magnitude.

Sex and Age Incidence of Hypertensive and Nonhypertensive Periarteritis Nodosa.—In table 1 it may be seen that many more men than women are included in all four groups. However, this disproportion is more pronounced in all three hypertensive groups than in the nonhypertensive one. These figures are uncorrected. Most necropsy series from general hospitals show a preponderance of males, usually in a ratio of about 2 to 1. It is suggested, therefore, that hypertensive periarteritis,

of both the primary and the secondary types, occurs in men more commonly than in women but that nonhypertensive periarteritis may be about equally common in both sexes.

It is striking that eight of the 11 cases of preexisting hypertension occurred in persons from 30 to 49 years of age, a period in which "malignant" hypertension is especially frequent. The group with secondary hypertension and the nonhypertensive group show a much more widespread age distribution. The group with initial hypertension is more like that with preexisting hypertension, in that 17 of the 35 subjects were in the age period from 30 to 49 years.

Incidence of Allergic Manifestations in Hypertensive and Nonhypertensive Periarteritis Nodosa.—About one fourth of the subjects in each of the three hypertensive groups had allergic manifestations (table 2). The incidence of such reactions in the nonhypertensive group was somewhat higher (38.7%). This difference may

TABLE 2.—*Incidence of Allergic Manifestations in Hypertensive and Nonhypertensive Periarteritis Nodosa*

	Group I Preexisting Hypertension		Group II Initial Hypertension		Group III Secondary Hypertension		Group IV No Hypertension		Total
	No.	%	No.	%	No.	%	No.	%	No.
With allergy	3	27.3	8	22.8	5	29.4	12	38.7	28
Without allergy	8	....	27	....	12	....	19	....	66

TABLE 3.—*Distribution of Arterial Lesions in Hypertensive and Nonhypertensive Periarteritis Nodosa*

No. of Organs and Structures Involved	Group I Preexisting Hypertension No. of Cases	Group II Initial Hypertension No. of Cases	Group III Secondary Hypertension No. of Cases	Group IV No Hypertension No. of Cases	Total No. of Cases
1-3	0	8	0	2	10
4-6	9	16	5	7	37
7-10	2	7	5	14	28
More than 10	0	4	7	8	19

not be great enough to be considered definitely significant, but there is at least suggestive evidence that periarteritis nodosa may develop in hypertensive, nonallergic persons more frequently than in nonallergic persons with normal blood pressures.

Distribution of Arterial Lesions in Hypertensive and Nonhypertensive Periarteritis Nodosa.—It is evident from table 3 that in the groups with preexisting and initial hypertension the arterial lesions tended to be limited to relatively few organs and structures, usually six or less. On the other hand, in the nonhypertensive group and in the one in which hypertension developed secondarily, the lesions were frequently widely disseminated throughout the body. Comparison of lesions in intra-abdominal and extra-abdominal structures discloses that the difference in distribution pertains chiefly to extra-abdominal locations. Within the abdomen arterial lesions are frequent, and about equally so, in all four groups (table 4). In the rest of the body, however, with the exception of the heart (table 5) arterial lesions are quite uncommon in the groups with preexisting or initial hypertension.

TABLE 4.—*Incidence of Arterial Lesions in Abdominal Viscera of Hypertensive and Nonhypertensive Periarteritis Nodosa*

Organ	Group I Preexisting Hypertension		Group II Initial Hypertension		Group III Secondary Hypertension		Group IV No Hypertension	
	No.	%	No.	%	No.	%	No.	%
Kidney	5	45.5	32	91.5	15	88.4	27	87.2
Liver	9	81.8	21	60.0	9	53.0	19	61.3
Pancreas	4	36.4	17	48.6	12	70.7	18	58.0
Adrenal gland	8	67.6	15	42.8	10	59.8	16	51.7
Spleen	3	22.2	9	25.7	9	53.0	11	35.5
Intestine	4	36.4	10	28.6	11	64.7	16	51.7
Gallbladder	4	36.4	11	31.4	5	29.4	5	16.1
Mesentery	1	9.1	13	37.2	8	42.0	6	19.3
Stomach	5	45.5	7	20.0	8	42.0	9	29.0

TABLE 5.—*Incidence of Arterial Lesions in Extra-Abdominal Viscera in Hypertensive and Nonhypertensive Periarteritis Nodosa*

Organ or Structure	Group I Preexisting Hypertension		Group II Initial Hypertension		Group III Secondary Hypertension		Group IV No Hypertension	
	No.	%	No.	%	No.	%	No.	%
Heart	6	54.5	20	57.1	14	82.5	23	74.2
Testis	2	25.0	9	29.0	9	60.0	3	14.3
Lung	1	9.1	7	20.0	6	35.3	7	22.6
Skeletal muscle	0	....	3	8.6	4	23.5	7	22.6
Peripheral nerve	0	....	5	14.3	2	11.8	4	12.9
Prostate	0	....	4	12.9	5	33.3	7	33.3
Urinary bladder	2	18.2	3	8.6	0	....	3	9.7
Vasa vasorum of aorta	1	9.1	3	8.6	2	11.8	3	9.7
Bronchi	0	....	2	5.7	1	5.9	1	3.2
Uterus	0	....	2	50.0	0	....	3	30.0
Peripheral arteries	0	....	1	2.9	0	....	4	12.9
Diaphragm	1	9.1	1	2.9	0	....	4	12.9
Seminal vesicle	0	....	1	3.2	0	....	3	14.3
Esophagus	0	....	0	....	2	11.8	5	16.1
Lymph node	1	9.1	1	2.9	3	17.6	5	16.1
Fallopian tube	0	....	1	25.0	0	....	3	30.0
Ovary	1	33.3	0	....	0	....	1	10.0
Epididymis	1	12.5	0	....	2	18.3	1	4.8
Retroperitoneal arteries	1	9.1	0	....	0	....	1	3.2
Laryngeal arteries	0	....	1	2.9	0	....	1	3.2
Spermatic cord	0	....	1	3.2	0	....	0	....
Brain	0	....	1	2.9	5	29.4	2	6.5
Trachea	0	....	1	2.9	0	....	0	....
Thyroid	0	....	2	5.7	1	5.9	1	3.2
Ureters	0	....	2	5.7	0	....	2	6.5
Bone marrow	0	....	1	2.9	1	5.9	1	3.2
Brachial plexus	0	....	0	....	3	17.6	1	3.2
Lumbosacral plexus	0	....	0	....	2	11.8	0	....
Internal mammary artery	0	....	0	....	1	5.9	0	....
Spinal cord	0	....	0	....	1	5.9	0	....
Skin	0	....	0	....	1	5.9	3	9.7
Pelvic structures	0	....	0	....	0	....	1	3.2
Sciatic nerve	0	....	0	....	0	....	1	3.2
Mediastinum	0	....	0	....	0	....	1	3.2
Parietal pericardium	0	....	0	....	0	....	2	6.5
Meninges	0	....	0	....	0	....	1	3.2
Eye	0	....	0	....	0	....	1	3.2
Temporal artery	0	....	0	....	0	....	1	3.2
No. of different organs and structures	10	....	22	....	19	....	33	....
Total no. of organs and structures	17	....	72	....	65	....	107	....
Total no. per case	1.5	....	2.1	....	3.8	....	3.5	....

In the nonhypertensive and secondarily hypertensive groups lesions were often widespread in the thorax, pelvis, head, neck and extremities. When the data are reduced to the average number of extra-abdominal structures involved per case, it may be noted that such lesions were twice as common in these groups. This finding suggests that in hypertensive periarteritis the inflammatory lesions tend to be restricted to the same organs in which degenerative arteriolar lesions are frequent, whereas in nonhypertensive periarteritis, while commonest in the same sites, lesions may nevertheless appear in any part of the body.

Histopathological Features of Hypertensive and Nonhypertensive Periarteritis Nodosa.—Review of the sections from the 28 necropsies on patients with periarteritis nodosa in the Bellevue Hospital series failed to disclose any distinctive differences in the characteristics of the arterial lesions in the hypertensive as compared with the nonhypertensive cases. In the latter group the lesions tended, however, not only to be more widespread but also to be more numerous in the involved organs. In the group with antecedent hypertension the lesions were confined mainly to small arteries and arterioles. Large vessels, as well as small ones, were more frequently involved in the nonhypertensive and secondarily hypertensive groups.

COMMENT

The differences observed in the foregoing analysis between hypertensive and nonhypertensive cases of periarteritis nodosa are not striking when considered individually. The differences are relative rather than absolute. When grouped together, however, these differences do suggest that the general pattern of the disease process is influenced by the absence or presence of hypertension. Zeek, Smith and Weeter,[10] in their comparison of hypersensitivity and nonhypersensitivity arteritis, noted some of the same differences that we observed in our nonhypertensive and hypertensive groups. In the present study we did not find that these differences were based on the presence or absence of demonstrable hypersensitivity or that the differences were sufficiently striking to justify the view that periarteritis nodosa without hypersensitivity is a distinct disease.

While it is not possible to determine from this analysis the exact percentage of cases of periarteritis nodosa with antecedent hypertension, the indications are that it was much higher than the 11.7% in which this condition was clearly present, and probably higher than can be accounted for by coincidence alone. This inference can be drawn from the fact that the large group of 35 cases in which hypertension was observed at the start of the terminal illness resembled the group with preexisting hypertension much more closely than it resembled the groups in which hypertension developed during the course of the disease or failed to occur. The majority of the cases in the group with initial hypertension were, therefore, probably ones in which hypertension had been present prior to the onset of periarteritis nodosa.

If hypertension can in some instances favor the development of periarteritis nodosa, as this study would indicate, it is important to inquire into the possible role of arterial blood pressure in the pathogenesis of this disease. Since the lesions of

10. Zeek, P. M.; Smith, C. C., and Weeter, J. C.: Studies on Periarteritis Nodosa: III. The Differentiation Between the Vascular Lesions of Periarteritis Nodosa and of Hypersensitivity, Am. J. Path. **24**:889-917, 1948.

periarteritis nodosa occur chiefly in the walls of blood vessels, it is reasonable to assume that some noxious agent capable of inciting the inflammatory reaction is carried in the blood stream. Since the lesions are restricted mainly to small arteries, it may be further assumed that the noxious agent can ordinarily penetrate in sufficient concentration only at these locations to produce the reaction. Arterial blood pressure may, therefore, be a factor in the entrance of injurious materials into the vessels walls.

If it is accepted that allergy is responsible for the origin of periarteritis nodosa, then the arterial lesions may be considered to be the result of antigen-antibody reactions in sensitized tissue, and the noxious blood-borne agent is probably either an antigen or its specific antibody. Most antigens and antibodies are large molecular substances, usually proteins, that do not readily pass through vessel walls at capillary or venous pressures. It is conceivable that at arterial pressures these materials can penetrate the arterial endothelium with greater facility and that their passage may be accelerated by hypertension. The frequent deposition of lipid and calcium compounds in arterial walls, contrasted with the rarity of such deposits in veins, suggests that the materials that enter arterial walls from the blood may differ from those that gain access at low pressure points in the vascular system. It is noteworthy that the deposition of lipid in arterioles is greatly increased in hypertension.[11]

The rapidity with which a sensitized guinea pig undergoes anaphylactic shock after intravenous injection of small amounts of antigen perhaps suggests that no particular barrier is imposed against the escape of antigenic substances from the blood. In such an experiment, however, the animal is at the peak of its sensitized state and the antigen, although small in quantity, is probably of far greater amount than that ever introduced spontaneously into the circulation at any one time. The delay period that may intervene between introduction of a "shocking" dose of antigen and the onset of anaphylaxis in a passively sensitized guinea pig probably provides a better indication of the slowness of permeation of antigen from the blood into the tissues. Indeed, this technique was used by Hopps and Lewis to measure the rate of escape of antigen from the circulation.[12] With their procedures a latent period of two to three hours followed the intravenous injections of antigen before anaphylactic shock occurred in the passively sensitized guinea pig. It is possible that during this period much of the antigen penetrated through arteries and arterioles rather than through capillaries.

The above interpretation is based largely on conjecture, but it provides a plausible explanation for the curious and otherwise inexplicable fact that the lesions of periarteritis occur almost exclusively in the arterial system. It has the further merit of explaining how both hypersensitivity and hypertension could participate in the development of this disease. It accounts for the differences noted in the cases with antecedent hypertension and those without it. The former may represent a group in which the hypersensitive state in itself would not be sufficiently pronounced to cause vascular lesions if it were not for the presence of an elevated blood

11. Wilens, S. L., and Elster, S. K.: The Role of Lipid Deposition in Renal Arteriolarsclerosis, Am. J. M. Sc. **219**:183-196, 1950.

12. Hopps, H. C., and Lewis, J. H.: Studies on Capillary Permeability as Affected by Anoxemia, Am. J. Path. **23**:829-836, 1947.

pressure to promote the entrance of reactive substances, either antigens or antibodies, into the arterial walls. Since hypertension produces most of its damaging effects in the splanchnic area, these vessel groups would be most severely involved.

A number of serious objections can be raised concerning the validity of this hypothesis. If the localization of lesions in arteries depends on penetration of reactive substances into the vessel walls at arterial pressures, one would expect that large elastic arteries and the left ventricular endocardium would be involved. Yet these sites are generally spared. It is possible that it is necessary for the inciting agent to penetrate to the adventitia before provoking the inflammatory response and that such complete penetration cannot be affected in large thick-walled arteries. Some support for this interpretation is provided by the fact that frequently the most intense reaction is found in the adventitia. This explanation does not account for the absence of lesions in the left ventricular endocardium. Moreover, it fails to explain the focal nature of the lesions.

It is also difficult to account for such a case as that reported by Old and Russell [4] of periarteritis limited to the pulmonary arteries. In pulmonary hypertension the blood pressure in the pulmonary arteries seldom rises to that in the ordinary systemic arteries. The negative intrathoracic pressure and the relative thinness of pulmonary arterial walls may favor the development of pulmonary arterial lesions at lesser degrees of arterial tension in these special circumstances. Nevertheless, it is difficult to explain the absence of systemic arterial lesions in this case, unless one further assumes that because of the associated cardiac malformation antigenic substances and antibodies failed to reach the general circulation in the same concentration as in the pulmonary circuit.

The explanation developed in this discussion is not presented as a well established theory that will account for all the phenomena associated with periarteritis nodosa but as a working hypothesis that can explain many of the features of the disease that are otherwise quite obscure. It is obvious that our understanding of this disease process will never be satisfactory until the distinctive distribution of lesions and the peculiar relationships to hypersensitivity and hypertension can be explained.

SUMMARY AND CONCLUSIONS

A review of 94 cases of periarteritis nodosa disclosed that in 46, or about one-half, hypertension was present on initial examination and in 11 of these there was a history of hypertension that antedated the onset of periarteritis nodosa. In 17 of the remaining 48 cases hypertension developed secondarily during the course of the disease.

Comparison of the groups with hypertensive and nonhypertensive periarteritis nodosa revealed the following differences:

1. The preponderance of men over women was more pronounced in all hypertensive groups than in the nonhypertensive one.

2. Antecedent hypertensive periarteritis nodosa occurred chiefly in the age period from 30 to 49 years; nonhypertensive and secondarily hypertensive periarteritis nodosa occurred with almost equal frequency at all ages.

3. A higher percentage of the group with nonhypertensive periarteritis nodosa had a history of allergic manifestations.

4. The arterial lesions of periarteritis nodosa in the group with antecedent hypertension tended (*a*) to be less numerous, (*b*) to involve smaller vessels and (*c*) to be less widespread in the various organs than in nonhypertensive group.

5. The arterial lesions of periarteritis nodosa in the group with antecedent hypertension were limited chiefly to the abdominal organs and the heart.

Comparison of the lesions in the group of 35 cases in which hypertension was present on initial examination, but in which a history of long-standing hypertension could not be obtained, revealed that the lesions resembled those in the group with antecedent hypertension much more closely than the lesions in the nonhypertensive group. It is suggested, therefore, that in the majority of this group of 35 cases hypertension was present before the onset of periarteritis nodosa. The association of antecedent hypertension with periarteritis is probably greater than can be accounted for by coincidence alone.

It is concluded, therefore, that there is a group of cases of periarteritis nodosa in which preexisting hypertension is an etiological factor. This group may range from 10 to 50% of all cases of periarteritis. While relative differences exist between this hypertensive group and the nonhypertensive one, there is little reason to believe that the two represent distinct disease entities.

A RATIONAL BASIS FOR THE USE OF LOW SODIUM, HIGH PROTEIN DIET THERAPY IN LAENNEC'S CIRRHOSIS

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DURING the past three years clinical and metabolic studies [1] on patients with Laennec's cirrhosis have demonstrated the value of diets high in protein and calories and low in sodium in the management of this disease. Diet therapy is only one part of the total regimen; other important features are rest, general supportive

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The opinions expressed in this paper are those of the authors and do not necessarily represent the official views of any governmental agency.

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From the Department of Medicine, University of Illinois College of Medicine, the Research and Educational Hospitals and the Medical Nutrition Laboratory, an installation under the jurisdiction of the Surgeon General, United States Army.

The human albumin used in this study was processed by the American National Red Cross from blood which it collected from voluntary donors. This is one of a series of investigations on human albumin being carried out with material supplied by the American National Red Cross. As soon as sufficient data become available to justify final conclusions concerning its therapeutic value, a full report to the medical profession on the use of human albumin in medical practice will be published.

1. Gabuzda, G. J.; Morey, G. R.; Scudamore, H. H.; Consolazio, C. F., and Kark, R. M.: Observations on the Effects of Human Salt-Poor Serum Albumin on Healthy Young Men and on Patients Suffering with Chronic Liver Disease, to be published. Shadaksharappa, K.; Keeton, R. W.; Kyle, R. H., and Calloway, N. O.: Excretion of Steroidal Substances by the Adrenal Cortex in Various Diseases, to be published. Vorhaus, L. J.; Scudamore, H. H., and Kark, R. M.: Measurement of Serum Cholinesterase Activity in the Study of Diseases of the Liver and Biliary System, Gastroenterology **15**:304-315 (June) 1950. Morey, G. R., and Kark, R. M.: A Comparison of Different Regimens in the Treatment of Hepatic Cirrhosis, J. Lab. & Clin. Med. **34**:1727-1728 (Dec.) 1949. Morey, G. R.; Paynter, C. R.; Consolazio, C. F.; Maloney, M. A.; Vorhaus, L. J.; Breimyer, M., and Kark, R. M.: Clinical and Metabolic Effects of Different Nutrients in Patients with Cirrhosis, Am. J. Med. **7**:408-409 (Sept.) 1949. Vorhaus, L. J.; Scudamore, H. H.; Gabuzda, G. J.; Morey, G. R.; Maloney, M. A., and Kark, R. M.: Serial Serum Cholinesterase Determinations in Liver Disease, J. Lab. & Clin. Med. **33**:1475-1476 (Nov.) 1948.

therapy and prohibition of alcohol and hepatotoxic drugs. All these are necessary to protect the liver from further damage, speed regeneration of hepatic cells, correct tissue wasting and restore hormonal and metabolic aberrations to normal. From the practical point of view it is not easy for the dietitian to provide a palatable high protein diet which is low in sodium without the use of special low sodium protein preparations. It appears, however, that this difficulty may be overcome by the oral use of ion exchange resins,[2] which absorb large amounts of sodium from the bowel and allow the cirrhotic patient to eat high protein diets containing salt.

Eisenmenger and his colleagues[3] have reported on the effects of rigid low sodium diets on patients with cirrhosis and ascites. Data from patients at this hospital confirm their observations. In the present communication, however, observations will also be reported which suggest, in the first place, that adrenal disturbances may play a major part in producing sodium retention in cirrhotic patients, and which show, in the second place, that tissue depletion from caloric and protein starvation is an important factor in the production of ascites.

METHODS

All patients were studied in the metabolic unit or outpatient clinic of the Research and Educational Hospitals. On admission to the study the majority of the cirrhotic patients were greatly underweight with clinical evidence of tissue depletion. In many, axillary and body hair was absent or scanty and low urinary sodium output was found. The latter was usually, but not always, reflected by waterlogging. Most of the patients had been imbibing alcoholic beverages to excess for many years. In the ward they ingested a nutritionally well balanced diet with fixed protein, caloric and sodium intakes which were varied according to the study being made. Fluid intake was also fixed, usually at 2.5 liters per day. In most of the studies the environment was kept constant in air-conditioned rooms. Metabolic balance studies were made by chemical analyses of food, feces and urine. Nitrogen, sodium, potassium, phosphorus, calcium, uric acid and creatinine levels were determined by standard procedures. Albumin and total protein were measured by the method of Campbell and Hanna,[4] and hematological studies were made on venous blood by standard Wintrobe techniques.[5] The eosinophils were counted by a modification of Randolph's method.[6] The 10 liver function tests which we employed have been outlined elsewhere.[1] Urinary 17-ketosteroids were measured by Robbie and Gibson's method[7] and urinary cortin by the method of Heard and Sobel.[8] Venous pressures and indirect portal pressures were measured with a phlebomanometer, using Davidson's technique.[9]

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2. Irwin, L.; Berger, E. Y.; Rosenberg, B., and Jackenthal, R.: The Effects of a Cation Exchange Resin on Electrolyte Balance and Its Use in Edematous States, J. Clin. Invest. **28**: 1403-1411 (Nov.) 1949. Kark, R. M., and Chapman, R. E.: Observations on Ion-Exchange Resins in the Management of Cirrhosis of the Liver, to be published.

3. Eisenmenger, W. J.; Ahrens, E. H.; Blondheim, S. H., and Kunkel, H. G.: The Effect of Rigid Sodium Restriction in Patients with Cirrhosis of the Liver and Ascites, J. Lab. & Clin. Med. **34**:1029-1038 (Aug.) 1949.

4. Campbell, W. R., and Hanna, M. I.: Albumin, Globulins and Fibrinogen of Serum and Plasma, J. Biol. Chem. **119**:15-33 (June) 1937.

5. Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1942.

6. Randolph, T. G.: Blood Studies in Allergy: I. The Direct Counting Chamber Determination of Eosinophils by Propylene Glycol Aqueous Stains, J. Allergy **15**:89-96 (March) 1944.

7. Robbie, W. A., and Gibson, R. B.: Rapid Clinical Determination of Urinary 17-Ketosteroids, J. Clin. Endocrinol. **3**:200-205 (April) 1943.

8. Heard, R. D. H., and Sobel, H.: Steroids: VIII. A Colorimetric Method for the Estimation of Reducing Steroids, J. Biol. Chem. **165**:687-698 (Oct.) 1946.

9. Davidson, C. S.; Gibbons, T. B., and Faloon, W. W.: Systemic and Portal Venous Pressures in Cirrhosis of the Liver, J. Lab. & Clin. Med. **35**:181-187 (Feb.) 1950.

EFFECTS OF SODIUM RESTRICTION IN CIRRHOTIC PATIENTS

Farnsworth [10] recently demonstrated that many patients with cirrhosis excrete small quantities of sodium in the urine. Some of our patients excreted less than 1 milliequivalent (23 mg.) of sodium per day in the urine and stool. There are, as far as we know, no data available on the sodium excretion from the skin in cirrhotic patients, but a normal person in a temperate environment excretes about 20 milliequivalents of sodium each day.[11]

In three cirrhotic persons (patients A. M., P. W. and B. F.) urinary sodium output on a low sodium diet increased from 21, 22 and 5 milliequivalents per day, respectively, when they were ill, to 44, 51 and 21 milliequivalents per day, respectively, when they were well. This indicates that the metabolic abnormality is reversible. Eisenmenger and associates [3] point out that when patients have improved on a rigid low sodium diet they eventually will tolerate considerable quantities of salt, and this has been true for our patients L. H. and K. K.

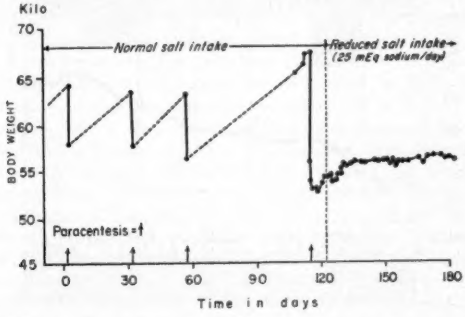

Fig. 1.—Effect of diet low in sodium (25 milliequivalents of sodium per day) in preventing accumulation of ascitic fluid after paracentesis in patient J. D. with cirrhosis of the liver.

In nearly all cirrhotic patients with ascites or edema adequate sodium restriction gives dramatic results. This is shown graphically in figure 1 (patient J. D.). The extent of sodium restriction required to maintain or produce "dry" weight varies with the individual patient. Patient J. N. reaccumulated water with an intake of 48 milliequivalents of sodium per day but remained "dry" with 24 milliequivalents per day. At present the critical level of sodium intake which prevents retention of water must be found for each individual patient by the method of trial and error. It is our custom to begin with diets which contain 25 milliequivalents of sodium per day.

In three patients with cirrhosis and coexisting renal disease, salt restriction produced a "low salt syndrome," [12] with muscle cramps, nausea, drowsiness and eventual uremic coma and death. Biochemical changes observed showed a decrease

10. Farnsworth, E. B.: Electrolyte Partition in Patients with Edema of Various Origins, Am. J. Med. **4**:338-342 (March) 1948.

11. Freyberg, R. H., and Grant, R. L.: Loss of Minerals Through the Skin of Normal Humans When Sweating Is Avoided, J. Clin. Invest. **16**:729-731 (Sept.) 1937.

12. Schroeder, H. A.: Renal Insufficiency Caused by Overhydration or Depression of Sodium Chloride: The "Low Salt Syndrome," J. Clin. Invest. **28**:809 (July) 1949.

in serum sodium to below 125 milliequivalents per liter, a fall in plasma carbon dioxide-combining power and a rising plasma nonprotein nitrogen value. Strauss and his colleagues [13] and Welt [14] have observed a similar clinical picture in patients with ascitic cirrhosis having normal renal function. These patients became confused and weak and displayed serious water retention, following repeated paracenteses, while living on a rigid sodium-restricted diet. This has not been seen in our clinic.

RESTORATION OF BODY TISSUE IN CIRRHOSIS

When sodium restriction is adequate, the "dry" weight of ascitic or edematous patients is nearly always found to be much below "best" weight. In figure 1 it can be seen that the "dry" weight of patient J. D. was 50 Kg. His best weight had been

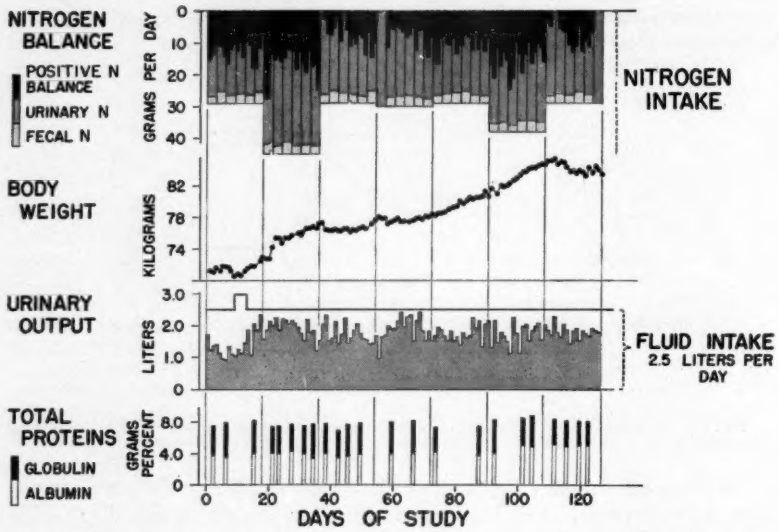

Fig. 2.—Effects of diet high in protein and low in sodium on the nitrogen balance, body weight, urinary output and serum albumin levels of patient A. M. with cirrhosis of the liver. Note long-continued positive nitrogen balance.

90 Kg. At present we do not have statistically significant data on the percentage of cirrhotic patients who show severe tissue wastage. Among 451 chronic non-cirrhotic alcoholics studied by us,[15] 20 per cent were grossly underweight. This is due to low caloric and protein intakes, as well as to the negative nitrogen balance induced by alcohol per se.[16] It is our impression that 80 per cent of our alcoholic cirrhotic patients show pronounced tissue depletion when they are "dried out."

13. Strauss, M. B.: Personal communication to the authors, 1950.

14. Welt, L.: Personal communication to the authors, 1950.

15. Figueroa, W. F.; Sargent, F., and Kark, R. M.: Lack of Avitaminosis Among Chronic Alcoholics: Its Relation to Fortification of Cereal Products and the General Nutriture of the Population, J. Clin. Invest. **19**:812 (June) 1950.

16. Mendel, L. B., and Hilditch, W. W.: The Influence of Alcohol upon Nitrogenous Metabolism in Men and Animals, Am. J. Physiol. **27**:1-23 (Nov.) 1910.

The restoration of tissue mass and the regeneration of liver cells require a high protein intake for maximal repair. Observations in our unit bear out Klatskin's [17] report that repair can and does take place on a "minimal" regimen providing 1 Gm. of protein per kilogram of body weight per day. However, on such a diet response to therapy is slow. Two and five-tenths grams of protein per kilogram of body weight per day has been found to be a satisfactory intake when one considers the appetite of the patient, the rate of repair and the ability of the dietitian to provide a high protein diet low in sodium. Figure 2 shows the effects of consumption of a well balanced diet providing each day twice the basal requirement for calories, between 181 and 300 Gm. of protein, 33 milliequivalents of sodium and 2.5 liters of fluid.

CASE HISTORY

A. M., a 32 year old alcoholic watchman suffering with cirrhosis, was admitted to the hospital. He appeared very ill with jaundice, edema of the feet and ankles and marked evidence of recent loss of weight. A number of telangiectases were noted on his face, shoulders and arms. There was no hair on his chest or in the axillas, and pubic hair was sparse. He shaved once a week. The liver was enlarged and firm; the spleen could not be palpated; ascites was not observed. The breasts were flat and normal in appearance. In the past two years he had had three severe hematemeses and one bout of jaundice with edema and ascites. The protein and caloric intake of food had been grossly inadequate for at least six months before admission. Results of liver function tests were abnormal. Total protein was 7.6 Gm., with 4.1 Gm. of albumin per 100 ml. The urinary and fecal sodium output was 20 milliequivalents per day. Urine output was between 1 and 1.25 liters per day. For the first two weeks of the study there was a positive nitrogen balance of 15 Gm. per day, but weight did not increase and fluctuated between 70 and 72 Kg. The urinary output was low at 1 to 1.5 liters per day, with sodium excretion of 21 milliequivalents. By the beginning of the second week, his urinary output began to increase and his weight climbed steadily. At the end of 100 days, he had gained 13 Kg. in body weight (85 Kg.) and his urinary output ranged between 1.5 and 2.75 liters. During his stay in the hospital there were, as can be seen, a strongly positive nitrogen balance and an increasing daily sodium output, which reached 51 milliequivalents in the last week. Albumin changed only slightly, reaching 4.9 Gm. per 100 ml., but the appearance of the patient changed greatly. Tissue wasting disappeared; he began to look fat, and hair began to grow on the face, chest and axillas and in the suprapubic region. Libido was restored. The liver shrank, and results of liver function tests returned to normal. At about the sixtieth day of study nutritional gynecomastia [18] was evident. This was transient and disappeared by the time he was discharged from the hospital. Since then he has remained teetotal; his body weight has been maintained; results of his liver function tests are normal, and he is an active and vigorous man. The most recent observations on the patient were made 18 months after discharge. He is now receiving a normal diet with normal salt intake and has not shown any evidence of waterlogging.

COMMENT

The gain in body weight in patient A. M. over the 128 days of metabolic study was 13 Kg. The total retention of nitrogen during this time was approximately 1,400 Gm. This 1,400 Gm. nitrogen gain is equivalent to approximately 45 Kg. of fat-free protoplasm (allowing a factor of 32 for conversion of nitrogen to proto-

17. Klatskin, G., and Yesner, R.: Factors in the Treatment of Laennec's Cirrhosis: I. Clinical and Histological Changes Observed During a Control Period of Bed-Rest, Alcohol Withdrawal, and a Minimal Basic Diet, J. Clin. Invest. **28**:723-735 (July) 1949.

18. Klatskin, G.; Salter, W. T., and Humm, F. D.: Gynecomastia Due to Malnutrition, Am. J. M. Sc. **213**:19-30 (Jan.) 1947. Morey, G. R., and Kark, R. M.: Transient Nutritional Gynecomastia in Treated Cirrhotic Patients, to be published.

plasm).[19] Thus, there is a discrepancy of 32 Kg. between actual body weight and calculated weight. It is believed that in A. M., who is representative of our tissue-wasted patients with cirrhosis, the gain in protoplasm without massive gain in weight was made possible by displacement of water from overhydrated malnourished tissue cells. In many of the patients a negative potassium balance was found in the face of a positive nitrogen balance, as well as a high urinary water output relative to water intake. It can be concluded in these circumstances that nitrogen from the food enters the cell to form protein and displaces an intracellular potassium brine. The loss of brine in the urine balances somewhat the gain in protoplasm.

THE PROBLEM OF FORMATION OF ASCITIC FLUID IN CIRRHOSIS

In view of the observation that restoration of tissue mass by high protein, low sodium feeding occurs through displacement of intracellular water and potassium, the question arises whether the chronically protein-depleted brine-filled cells of the cirrhotic patient may be responsible in part for formation of ascitic fluid. In addition it would be of value to know whether sodium retention in the urine of

TABLE 1.—*Some Factors Associated with Ascites in Chronic Liver Disease*

Increased pressure in portal venous system [20]
Decreased intraportal osmotic pressure due to reduction of total circulating albumin *
Increased hepatic lymph flow of albumin into the peritoneum †
An excess of antidiuretic factor [20]
Increased ferritin (vasodepressor substance) [21]
Retention of sodium ‡ due to hormonal imbalance ‡
Impairment of portal vein endothelium due to protein depletion of tissue (nutritional edema)

* Higgins, G.; Kelsall, A. R.; O'Brien, J. R. P.; Stewart, A. M., and Witts, L. J.: Quart. J. Med. **16**:263-274 (Oct.) 1947. Mankin, H., and Lowell, A.: J. Clin. Invest. **27**:145-153 (Jan.) 1948. James, A. H.: Clin. Sc. **8**:291-314 (Dec.) 1949.

† Volwiller, W.; Bollman, J. L., and Grindlay, J. H.: Proc. Staff Meet., Mayo Clin. **25**:31-33 (Jan.) 1950.

‡ Thorn, G. W., and Emerson, K., Jr.: Ann. Int. Med. **14**: 757-769 (Nov.) 1940. Kark and others.[21]

cirrhotic patients is conditioned by adrenal mineralocorticoid overactivity. In table 1 are shown some of the factors concerned with the formation of ascitic fluid. In regard to this we wish to point out that at present one cannot implicate any single specific pattern of disturbance in cirrhosis which initiates and maintains water imbalance resulting in ascites. There has been reported in the literature, and we have observed in our clinic, ascites in cirrhotic patients with normal serum albumin levels; low albumin levels in cirrhotic patients without ascites, and failure of ascites to clear when extremely low albumin levels have been restored to normal levels by massive infusions of human albumin. Many patients with cirrhosis have severe portal hypertension, as shown by esophageal varices and hemorrhoids, but no evidence of ascites. One of our patients, as we shall show below, cleared his ascites as a result of diet therapy but showed high portal pressure months later when this was measured with a phlebomanometer. Patients may also have a good urinary output in relation to water intake in the face of ascites, which is contrary to the

19. Reifenstein, E. C., Jr.; Albright, F., and Wells, S. L.: The Accumulation, Interpretation, and Presentation of Data Pertaining to Metabolic Balances, Notably Those of Calcium, Phosphorus, and Nitrogen, J. Clin. Endocrinol. **5**:367-395 (Nov.) 1945; correction **6**:232 (Feb.) 1946.

suggestions of Ralli [20] and Mazur and Shorr.[21] It, therefore, seems likely that in the individual patient a subtle combination of different physiological disturbances develops which forces, or allows, water, electrolyte and serum protein to pass into, or collect in, the peritoneal cavity. Evidence that tissue wasting may produce and maintain ascites is shown in figures 3 and 4 for patient K. K.

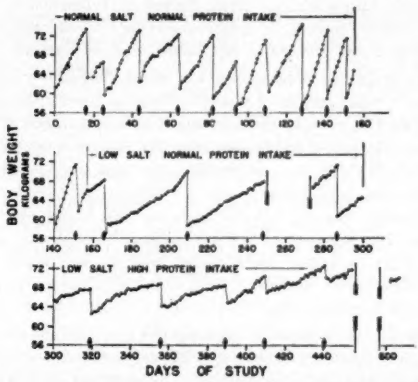
NORMAL SALT NORMAL PROTEIN INTAKE
LOW SALT NORMAL PROTEIN INTAKE
LOW SALT HIGH PROTEIN INTAKE
BODY WEIGHT
DAYS OF STUDY

Fig. 3.—Fluctuations in body weight in patient K. K. with cirrhosis. Note rapid gain of weight after paracenteses (indicated by arrows) when diet contained abundant salt and normal amount of protein, the slow gain after paracenteses when diet restricted sodium and provided a normal protein content and the disappearance of ascites and gain in body weight when a high protein, low salt diet was consumed.

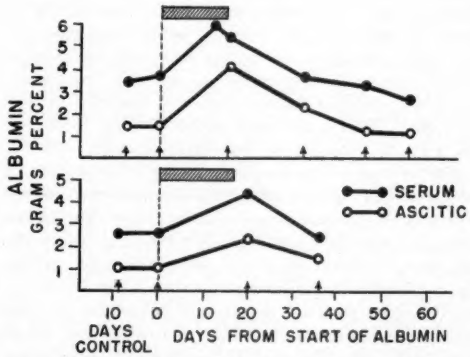

Fig. 4.—Effect of intravenous infusion of 1,000 Gm. of human serum albumin on serum and ascitic fluid albumin in patient K. K. (upper part) and patient L. F. (lower part) with cirrhosis. Time of infusion is indicated by cross-hatched area. Paracenteses are indicated by arrows.

20. Ralli, E. P., and Leslie, S. H.: The Role of the Posterior Pituitary in the Production of Ascites Associated with Cirrhosis of the Liver, in Soskin, S.: Progress in Clinical Endocrinology, New York, Grune & Stratton, Inc., 1950, pp. 557-562.

21. Mazur, A., and Shorr, E.: Hepatorenal Factors in Circulatory Homeostasis: IX. The Identification of the Hepatic Vasodepressor Substance, VDM, with Ferritin, J. Biol. Chem. **176**:771-787 (Nov.) 1948.

CASE HISTORY

K. K., a 65 year old alcoholic bookkeeper ill with cirrhosis, has been observed for the past three years. In April 1947 he was admitted with severe tissue wasting, slight jaundice, ascites and edema. In the abdominal wall venous collateral drainage was apparent. The liver was enlarged well into the epigastrium, hard and finely irregular over the surface, with a firm edge. It was slightly tender. A biopsy specimen showed cirrhosis. The spleen was moderately enlarged and slightly tender. Tests showed liver function to be severely impaired, and the results have been reported in detail elsewhere.[1] Roentgenographic study of the gastrointestinal tract, chest and bones was not remarkable. There was slight osteoporosis.

During his 460 days in the metabolic unit he was studied intensively and has been readmitted on occasion since then for short periods of restudy. Four dietary regimens have been employed. First, from day 1 to day 153, the diet provided the basal requirements plus 60 per cent of the requirements for calories, 1 Gm. of protein per kilogram of body weight and sodium ad libitum. Second, from day 154 to day 299, the diet provided the basal requirement plus 60 per cent of the requirements for calories, 1.50 Gm. of protein per kilogram of body weight and restriction of sodium to 33 milliequivalents per day. Third, from day 300 to day 460, the diet provided the basal requirement plus 100 per cent of the requirement for calories, 33 milliequivalents of sodium per day and a protein intake which varied between 2.50 and 4 Gm. per kilogram of body weight. The fourth period was after he had been discharged from the hospital, when he took his meals mainly in restaurants.

During the first period he required 11 paracenteses (fig. 3) and received two courses of albumin therapy, which provided, respectively, 1,600 and 1,450 Gm. of albumin. The urinary output at this time was 1,540 ml. per day on a fixed intake of 2.50 liters of fluid. The serum albumin increased from 3.5 to 5.4 Gm. per ml., but no diuresis occurred. In fact, the infused albumin escaped into the peritoneal cavity, raised the level of ascitic albumin from 1.1 to 3.8 Gm. per 100 ml. and reaccumulated ascitic water more rapidly than usual (fig. 4). During the second period of diet therapy the low salt intake apparently slowed the reaccumulation of ascitic fluid in a remarkable way, only four paracenteses being required. However, "dry" body weight ("dry" weight is the lowest body weight after all ascitic fluid has been removed from the abdomen by paracentesis) did not show much change. During these first two periods of study the patient's condition improved, the liver showing evidence of regeneration by the development of large masses of new cells, masses which could be easily felt on the surface. Results of liver function tests also improved somewhat, but the patient remained wasted and thin. During the third period of study there were a long-continued remarkably positive nitrogen balance and high urinary water (2,510 ml. per day) and potassium output, with gradual disappearance of ascites. The quantity of fluid withdrawn from the abdomen was less at each of the five paracenteses made at this time. The final taps were dry. Just prior to the last paracentesis the patient was infused with 900 Gm. of albumin intravenously. No extra fluid was drawn into the peritoneal cavity at this time as had previously occurred, since movement of infused albumin into the peritoneal cavity did not take place. On the five-hundredth day he was discharged and has not collected any ascitic fluid since. During the third study of 128 days with intensive diet therapy "dry" weight increased by 13 Kg. Body contours rounded, and his collars and shirts became too small. Tissue wasting disappeared. His liver was now studded with large orange-sized regenerated nodules, and results of liver function tests had returned to normal. After discharge he returned to light work. His meals were taken mainly in restaurants and consisted of standard protein foods. He avoided salty foods and table salt but obviously had a much higher intake of sodium than when he was in the hospital. He was readmitted on four occasions for follow-up study. No ascitic fluid could be found up to 14 months after discharge (eight hundred and eightieth day of the study). Liver function test results were within normal limits. However, venous collateral drainage was apparent on his abdomen with cephalad flow of blood. Venous pressure in the arm veins was normal at 70 ml. of water, but it was elevated in the abdominal collateral veins to 180 ml. of water.

COMMENT

The salient features in patient K. K., as described above, were, at the beginning, tissue wasting with cirrhosis and portal hypertension. There was an increased permeability of the endothelial lining of the mesenteric vascular bed to albumin, so that infused albumin passed through the cells and into the peritoneal cavity, where it bound water. Although a low salt intake slowed down the rate of reaccumulation of ascitic fluid, body tissue and cellular protein depletion was not repaired. During the period of high protein feeding the patient laid down tremendous quantities of protoplasm and excreted more urine than the daily intake of fluids. At the same time the output of potassium was high in relation to intake. The obvious interpretation is that the retained nitrogen was laid down as protoplasm and forced a potassium-rich brine out of the cells, or out of both the cell and the extracellular spaces. Serum potassium levels, however, did not drop. It is most unlikely that the retained nitrogen could have been retained in the circulation, nor could it have been stored as urea, amino acids or polypeptides.[22]

In discussing the question of the genesis of ascites or edema, great attention has been paid by nearly all authors to the concept of differential osmotic pressure between the circulation and the extracirculatory spaces. Armstrong [23] states:

> Measurements of the effective serum osmotic pressure (i. e., the pressure developed by serum against the protein-containing ascitic fluid simultaneously obtained) have indicated that when this variable is . . . below [a] critical level, ascitic formation resumes.

This is an important concept.

In most discussions dealing with the formation of edema, variations in the permeabilities of the membranes, across which albumin, water and electrolyte have to pass to reach an extracirculatory space (such as the peritoneal cavity), have been neglected. For instance, there are pronounced physiological differences in the permeability of naturally healthy membranes (e. g., red blood cell, the cornea). In general when tissue depletion is obvious the protein content of individual cells and, therefore, of membranes such as vascular endothelium must be decreased. If this happens, then the protoplasmic gel within the cell and protein capsule of the cell wall must be thinner and more liquid than the firm gel of a healthy cell. The data presented are evidence that in depleted cirrhotic patients the endothelial cells are depleted of protein and overhydrated. Da Costa has studied tissue depletion in rats and has observed that body cells lose protein and become waterlogged when animals are starved.[24] In patient K. K. circulating albumin was not abnormal, and this too is a common finding in starvation, and even in starvation with edema.[25] His portal pressure was high initially, and when ascites had disappeared it still remained high. If we accept Kelty's [26] concept that regeneration of liver lobules in cirrhotic patients increases portal hypertension, then the portal pressure in patient K. K. should have been at a higher level when he was well than early in his disease.

22. Kosterlitz, H. W., and Campbell, R. M.: The Storage of Protein in the Adult Animal, Nutrition Abstr. & Rev. **15**:1 (July) 1945.

23. Armstrong, S. H., Jr.: Mechanism of Action of Serum Albumin Therapy in Internal Medicine, Am. J. Med. **4**:390-397 (March) 1948.

24. Da Costa, E.: Personal communication to the authors, 1950.

25. Keys, A.; Taylor, H. L.; Mickelsen, O., and Henschel, A.: Famine Edema and Mechanism of Its Formation, Science **103**:669-670 (May 31) 1946.

26. Kelty, R. H.; Baggenstoss, A. H., and Butt, H. R.: The Relation of the Regenerated Hepatic Nodule to the Vascular Bed in Cirrhosis, Proc. Staff Meet., Mayo Clin. **25**:17-25 (Jan.) 1950.

Our observations lead us to believe that ascites from tissue depletion is common in patients with cirrhosis. Figure 5 is a schematic drawing of our concept of the production and cure of tissue-depletion ascites in cirrhosis.

THE ADRENAL GLAND IN CIRRHOSIS

The possibility exists that retention of sodium in cirrhosis is due to overproduction, or overactivity, of adrenal mineralocorticoids. In this regard Daughaday and MacBryde [27] have recently discussed in detail the various theories of sodium

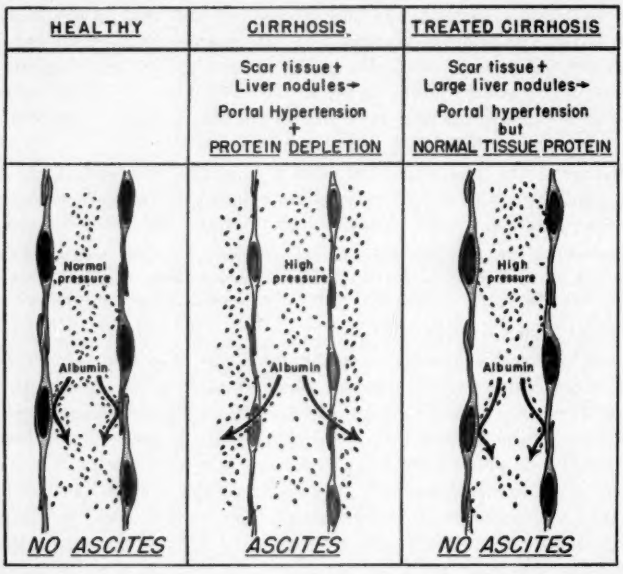

Fig. 5.—A schematic drawing of the concept of production and cure of tissue-depletion ascites in cirrhosis of the liver: Left (no ascites), in healthy men and animals portal pressure is low; the endothelial cells of the mesenteric portal capillaries are filled with protein, and these are impermeable to albumin. There is no ascites. Even if portal pressure is raised by ligature of the portal vein, ascitic fluid will not collect. This is true for men and for the experimental animal. In the latter ascites will develop only when portal ligature is followed by protein depletion through plasmapheresis. Center (ascites), in cirrhosis the scar tissue and pressure of regenerating lobules cause portal hypertension. Initially no ascitic fluid forms, but as tissue depletion develops the vascular endothelial cells lose protein and gain electrolyte and water. Under pressure circulating serum albumin molecules, as well as infused albumin (see also fig. 4), penetrate the thin protein gel of the vessel wall and, going into the peritoneal cavity, retain water and salt there. This also explains why many patients have ascites without peripheral edema: for in the periphery although the endothelial lining cells of the veins are also protein depleted, pressure is not raised. Right (no ascites), when tissue wasting is repaired by diet therapy then endothelial cells gain protoplasm and lose their intracellular potassium brine. Thereafter, although portal pressure remains high, the protein-filled cells once more become a barrier to circulating albumin. Ascitic fluid disappears and does not reaccumulate so long as protein nutrition remains normal (see case histories of K. K. and A. M., also figs. 2 and 3).

27. Daughaday, W. H., and MacBryde, C. M.: Renal and Adrenal Mechanisms of Salt Conservation: The Excretion of Urinary Formaldehydogenic Steroids and 17-Ketosteroids During Salt Deprivation and Desoxycorticosterone Administration, J. Clin. Invest. **29**:591-601 (May) 1950.

reabsorption in relation to adrenal or renal overactivity. On the other hand, Lloyd and Williams [28] have reported adrenal insufficiency in patients with Laennec's cirrhosis, and, with other authors,[29] have observed 17-ketosteroid excretion to be low. Certainly, relative adrenal hypofunction is to be expected in cirrhosis, if only on the basis of protein deficiency producing pituitary depression with reduction of pituitary adrenocorticotropic hormone (ACTH) production. In table 2 are shown daily urinary excretion of 17-ketosteroids and cortin in six male patients with cirrhosis. The 17-ketosteroids are very low, below levels expected from eunuchoid persons. This implies adrenal hypofunction in relation to "nitrogen-fixing" hormone. On the other hand, the urinary cortin excretion in the cirrhotic patients was elevated, the normal range in this laboratory being 1 to 2 mg. per 24 hour excretion. The high values found may be due to overproduction or to failure of "detoxification," but no data are available on this score. The method used in our laboratory to measure "cortin" may measure mineralocorticoids as well as "sugar" hormone. Unfortunately, there is at present no satisfactory method for measuring urinary mineral-retaining (11-desoxy) adrenal compounds. A number of attempts have

TABLE 2.—*Twenty-Four Hour 17-Ketosteroid and Cortin Excretion in Urine from Six Patients with Cirrhosis of Liver*

Patient	Age	Sex	Blood Pressure Mm. Hg	Urinary Cortin, Mg. per 24 Hr.	Urinary 17-Keto-steroids, Mg. per 24 Hr.	Eosinophils per Cu. Mm.
L. F.	58	M	116/68	4.5	1.6	100
T. W.	58	M	118/62	3.8	0.75	140
K. K.	54	M	112/72	3.3	1.8	343
A. M.	32	M	98/56	4.3	1.2	66
P. W.	52	M	108/62	5.7	2.2	121
B. F.	60	M	128/70	3.8	1.4	143

been made to measure these by published procedures, but satisfactory data could not be obtained. Until such tests are available one can but speculate on the effects of endogenous adrenal steroid as a cause of salt retention and waterlogging in cirrhosis. The observation that adrenal dissociation occurs in cirrhosis is not too surprising in view of Greep and Deane's studies on the rat.[30] They believe that in this animal the zona glomerulosa of the adrenal produces desoxycorticosteroids, and the zonae fasciculata and reticularis, the 11-oxycorticosteroids. The zona glomerulosa in rats is not affected by administration of ACTH or by pituitary ablation but atrophies after injection of desoxycorticosterone acetate. On the other hand, the zonae fasciculata and reticularis atrophy with pituitary ablation or injection of cortisone and hypertrophy after injection of ACTH.

Because of the inability to measure mineral-retaining steroids in cirrhotic patients, it was decided to test adrenal activity in these patients by injection of

28. Lloyd, C. W., and Williams, R. H.: Endocrine Changes Associated with Laennec's Cirrhosis of the Liver, Am. J. Med. **4**:315-330 (March) 1948.

29. Gilder, H., and Hoagland, C. L.: Urinary Excretion of Estrogens and 17-Ketosteroids in Young, Adult Males with Infectious Hepatitis, Proc. Soc. Exper. Biol. & Med. **61**:62-65 (Jan.) 1946.

30. Greep, R. O., and Deane, H. W.: The Cytology and Cytochemistry of the Adrenal Cortex, Ann. New York Acad. Sc. **50**:596-615 (June) 1949.

ACTH and cortisone during low sodium and high sodium intakes and also to note the effects of salt loading on adrenal function. Details of these observations will be published elsewhere.[31] Below are details regarding several pertinent observations.

EFFECTS OF ACTH AND CORTISONE INJECTION IN PATIENTS WITH CIRRHOSIS

In figures 6 and 7 are shown the effects of injection of ACTH in a patient with cirrhosis and ascites during a low sodium, high protein regimen. These are compared with the effects of salt loading while the patient received a low sodium diet. In figure 8 are shown the effects of injection of cortisone into a cirrhotic patient during a low sodium, high protein diet.

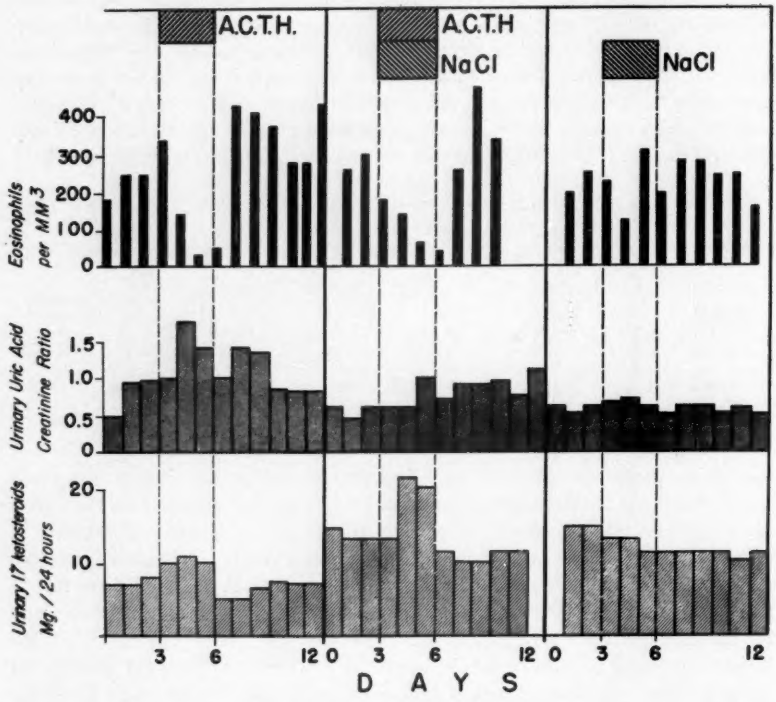

Fig. 6.—Effect of salt loading, injection of ACTH and injection of ACTH during salt loading on the eosinophil count, uric acid-creatinine ratio and 17-ketosteroid excretion of patient R. D., with cirrhosis, subsisting on a high protein, low sodium (22 milliequivalents) intake.

31. Kark, R. M.; Keeton, R. W.; Chapman, R. E.; Calloway, N. O.; Kyle, R. H.; Dyniewicz, J. M.; Weigand, G. F., and Consolazio, C. F.: Observations on Laennec's Cirrhosis: The Effects of ACTH and Cortisone During Low and High Sodium Regimens, to be published.

CASE HISTORIES

R. D., a 32 year old white truck driver who had been drinking heavily for 17 years, was admitted to the hospital following three paracenteses by his personal physician. On admission he had ascites, edema and a large firm, finely irregular liver palpable after paracentesis. There was little or no hair on his chest, in the axillas or in the suprapubic area. He shaved once a week and was without sexual desire. Pellagrous lesions of the scrotum, perineum and mouth were present. Tissue wasting was obvious, and liver palms and telangiectases were noted. Liver function was disturbed, the tests showing gross hepatocellular impairment. The serum albumin was 4.1 Gm. and the total protein 7.1 Gm. per 100 ml. Serum

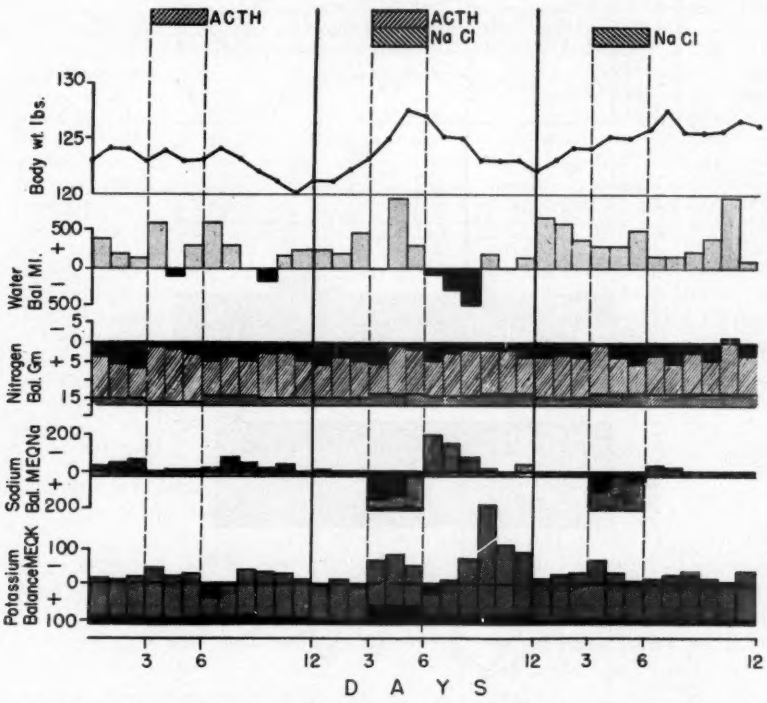

Fig. 7.—Effect of salt loading, injection of ACTH and injection of ACTH during salt loading on the body weight and on water, nitrogen, sodium and potassium balances in patient R. D., with cirrhosis, subsisting on a high protein, low sodium (22 milliequivalents) intake.

sodium was 136 and serum potassium 3.8 milliequivalents per liter. Ascitic albumin measured 1.6 Gm. per liter, ascitic sodium 153 milliequivalents and ascitic potassium 4.3 milliequivalents per liter. The hematocrit was 39 per cent and the hemoglobin concentration 14.9 Gm. per 100 ml. In the hospital he was treated with rest in bed and a diet which provided twice the basal requirements for calories, 2 Gm. of protein per kilogram of body weight and 22 milliequivalents of sodium per day. The pellagrous lesions responded within four days to twice daily intramuscular injections of a water-soluble B vitamin mixture and oral administration of B complex vitamins. Ascitic fluid did not reaccumulate, and a small amount remained in the peritoneal cavity. His condition improved slowly, and after 42 days in the metabolic unit it was decided that he had reached a "steady state" for study. Three metabolic and clinical

investigations were made. The first tested the effects of 100 mg. of ACTH given in four doses of 25 mg. per day for three days. The second tested the effects of the ACTH (given on the same schedule as in the first study) plus simultaneous oral therapy with 10 Gm. of sodium chloride per day for three days. The third tested the effects of administration of 10 Gm. of sodium chloride per day for three days. Each of the three studies consisted of a three day control period, a three day therapy period and a six day poststudy period. The diet remained

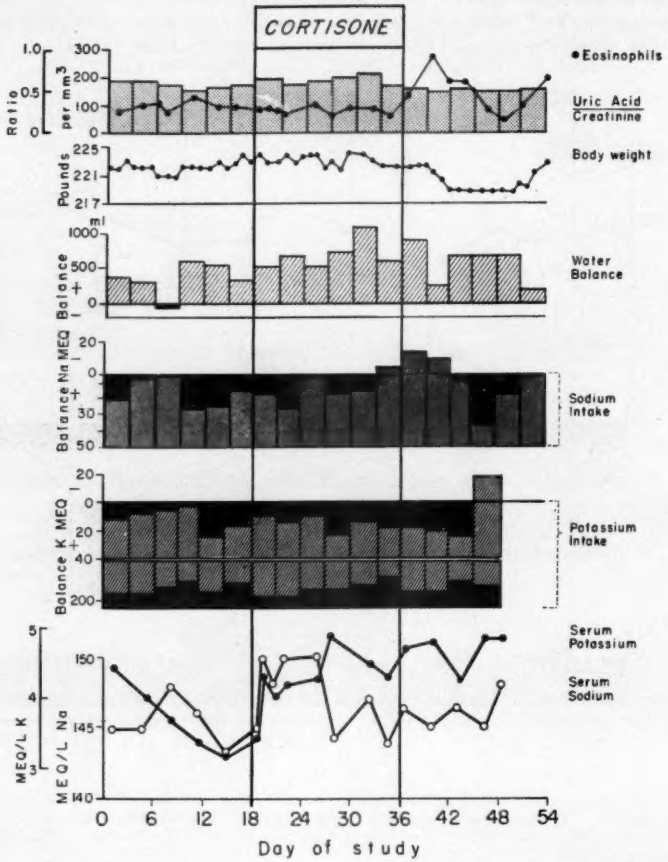

Fig. 8.—Effect of injection of cortisone on eosinophil count; uric acid-creatinine ratio; body weight, water, sodium and potassium balances, and serum sodium and potassium levels of patient W. McD., with cirrhosis of the liver, subsisting on a high protein, low sodium (50 milliequivalents) diet.

constant throughout the studies. The metabolic data are shown in figures 6 and 7. Clinically there was no improvement in the cirrhosis as a result of ACTH injection, nor did results of liver function tests change significantly. Alteration in plasma and ascitic protein moieties and in plasma and ascitic sodium and potassium, increase in urinary red blood cells, negative ascorbic acid balances and changes in venous and portal pressure resulting from ACTH injection will be presented elsewhere.[31]

W. McD., a 45 year old policeman, attended the outpatient clinic because of hemorrhoids. On examination he was found to have a large liver extending below the umbilicus. He admitted that he had been taking at least five or six alcoholic drinks each day for months but stated that he had been eating well. The hemorrhoids had been present for four years. When he was admitted to the ward, physical examination revealed a sallow-looking man with several spider nevi about the head and chest. There was a question of gynecomastia, but no biopsy was made. The abdominal wall was covered with fat, but there was no clinical evidence of ascites. The liver was somewhat irregular at the edge and enlarged about 4 inches (10 cm.) below the right costal margin in the right midclavicular line. The spleen was not palpated. The roentgenologic studies of the gastrointestinal tract and chest revealed nothing abnormal. Severe disturbance of liver function was present, with evidence of hepatocellular damage. A diagnosis of alcoholic Laennec's cirrhosis was made. In the ward he was placed on a diet which provided each day the basal requirement plus 100 per cent of the requirements for calories, 2.50 Gm. of protein per kilogram of body weight, 40 milliequivalents of sodium and 2.5 liters of water per day. He improved slowly, and after he had been in the ward for 62 days it was decided that he had reached a "steady state" for study. During the 18 day control period extensive metabolic studies were done on balances of nitrogen, calcium, phosphorus, sodium, potassium and ascorbic acid. Urinary uric acid and creatinine were measured, and various measurements were made of his blood, including hemograms, direct eosinophil counts, levels of calcium, phosphorus, sodium, potassium, alkaline phosphatase, ascorbic acid, uric acid, cholesterol, cholesterol esters and nonprotein nitrogen and carbon dioxide-combining power. These studies were continued during an 18 day period, when he was given 100 mg. of cortisone per day intramuscularly. Thereafter he remained in the metabolic study for the 18 day post-therapy period. During cortisone therapy, the patient had mental depression with crying and emotional outbursts. His liver became extremely hard and somewhat enlarged. The liver returned to normal size and consistency 10 days after cortisone therapy was stopped.

In two other patients with cirrhosis who were studied with cortisone administration a similar enlargement of the liver was observed during the period of therapy. Detailed metabolic studies on these patients will be reported elsewhere. Pertinent data on W. McD. are shown in figure 8.

COMMENT

The role of the adrenal gland in edema formation is not clear. Our studies, presented here for cirrhotic patients, indicate that the adrenal cortex has a vital role in the retention of water and salt.

In patient R. D. (figs. 6 and 7) there is evidence that salt loading alone (10 Gm. per day) caused only a rise in body weight with water retention of minimum quantity. The 17-ketosteroids, eosinophils, nitrogen balance, uric acid-creatinine ratio, serum sodium and serum potassium showed essentially no change. When R. D. was given the same basal regimen and received four 25 mg. doses of ACTH intramuscularly per day for three days, significant metabolic alterations occurred which influenced the course of the fluid and ionic balances.

There was a rapid drop in the eosinophils with a rise in the uric acid-creatinine ratio. The 17-ketosteroid excretion rose during the administration of the ACTH, then dropped when use of the drug was discontinued. The sodium excretion decreased during the ACTH therapy, then rapidly rose after its cessation, falling to an approximate balance on the sixth post-treatment day. The potassium output rose during the administration and fell to a positive balance for two days after ACTH therapy. The nitrogen balance remained positive, but the retention sharply decreased.

When ACTH and sodium chloride were given under the same conditions to the same patient after a control period of 10 days, there was again a precipitous drop in eosinophils, with a slight rise in the uric acid-creatinine ratio. The ketosteroids

rose during the administration of the ACTH and sodium chloride and afterward fell to levels below those of the control period. A rapid gain in body weight occurred during ACTH and salt therapy, followed by a loss after the administration of the two drugs. There was a sharp retention of water, followed by a loss which accompanied the changes in body weight. Nitrogen retention decreased during the administration of the ACTH and sodium chloride. There was a marked retention of sodium on this regimen, followed by increased excretion after the administration of sodium chloride and ACTH was stopped.

Potassium showed an opposite type of response. Excretion was increased during therapy, followed by a decrease after the administration of the drugs.[32]

INFLUENCE OF CORTISONE ON METABOLISM OF THE CIRRHOTIC PATIENT

When a second patient (W. McD.) was placed on essentially the same regimen and was given 100 mg. of cortisone per day for 18 days, very similar changes were noted when the data were compared. The fall in eosinophils was not significant, although there was a slight rise in the uric acid-creatinine ratio during the administration of cortisone. However, as expected, a sharp rise in the eosinophil count took place when the use of cortisone was discontinued, followed immediately by a drop in the eosinophils. This was accompanied with no significant change in the sodium until the end of the cortisone period, at which time there was a sudden rise in sodium retention extending into the postcortisone period for six days, followed by a period of equal negative balance, so that the net effect was no retention of sodium at all. Similar changes were noted in the weight, which increased during cortisone administration, then decreased below the level of the control period. The water balance became more negative during the cortisone treatment and only slowly returned to the control level.

INTERPRETATION OF THE EFFECTS OF TREATMENT WITH CORTISONE, ACTH, SODIUM CHLORIDE AND ACTH AND SODIUM CHLORIDE TOGETHER

It is obvious that our knowledge of the role of the adrenal gland in edema formation is so meager and our data are so limited that we cannot offer any final solution to the problem. However, since we do have certain indications of the behavior of the adrenal gland in cirrhosis, we wish to present a hypothesis which may serve as a working basis for future observations. There is no evidence here that these changes are the result of an antidiuretic substance. The urine did not become concentrated, and there is no evidence that the predominant feature is water reabsorption. Instead, the evidence points to sodium reabsorption in the kidneys as the primary mechanism of the sodium and fluid retention. This leaves the adrenal gland as the primary endocrine organ which has been active in the response to ACTH administration.

In the patients given alone, ACTH, ACTH with sodium chloride and sodium chloride the eosinophils increased after the administration of the drugs was stopped. Similar changes occurred with the use of cortisone, although there was no depression of the eosinophils during its administration.

32. Forsham, P.; Thorn, G.; Prunty, F. T. G., and Hills, A. G.: Clinical Studies with Pituitary Adrenocorticotropin, J. Clin. Endocrinol. **8**:15-66 (Jan.) 1948.

The other constant finding in these patients was the retention of sodium following the discontinuance of treatment with the drug. These two observations we interpret to indicate that in both instances there was relative adrenal cortex depression. In the case of cortisone therapy there was direct depression, as has been suggested by others.[33] In the case of the ACTH treatment there was pituitary depression with hypofunction so that when use of the substance was discontinued a temporary decrease occurred in the endogenous ACTH with secondary adrenal hypofunction. It would seem that the mechanism of the salt retention following the administration of ACTH and cortisone was that the mineral-retaining corticoids from the zona glomerulosa suddenly came into an imbalance with the 11-oxysteroids from the inner layers of the gland.

SUMMARY

There is a rational basis for the use of low sodium, high protein diets in the treatment of patients with cirrhosis of the liver. The high protein diets correct tissue depletion and build an endothelial protoplasmic barrier against high portal pressure. This prevents the formation of ascite fluid. Sodium retention is perhaps mediated by an adrenal dissociation, which dissociation has been demonstrated. It is emphasized that many factors are operative in the formation of ascitic fluid. Protein depletion and sodium retention are only two of these.

ABSTRACT OF DISCUSSION

DR. J. A. LUETSCHER, JR., San Francisco: The chief aim of treatment in hepatitis and cirrhosis is the repair of the damaged liver, and the most important weapon is a diet high in calories, protein and vitamins. Meanwhile, we may have to cope with serious complications, such as hemorrhage or coma, or with the debilitating effects of intractable ascites and edema, which interfere with dietary treatment.

Treatment with concentrated human serum albumin often is helpful when the patient's serum albumin level is low and when generalized edema is present. The risk of hemorrhage from an esophageal varix after too large or too rapid an infusion of albumin must be considered.

Limitation of sodium intake may help to reduce the rate of formation of ascitic fluid. On the other hand, there are patients who continue to form ascitic fluid at a rapid rate even when the sodium intake is very low. Frequently, repeated paracenteses in a patient on a very low sodium intake lead inevitably to sodium depletion. The administration of mercurial diuretics may be hazardous in such patients.

The mechanisms of formation of ascitic and edema fluid include not only the high portal venous pressure and the lowered colloid osmotic pressure of the plasma, but renal factors as well. In common with the edema of nephrosis and cardiac failure, the ascites of cirrhosis is related to a diminished ability of the kidneys to excrete sodium and water. It can be demonstrated by biologic assay that such patients may excrete abnormally large amounts of antidiuretic and antinatruretic substances resembling the secretion of the posterior portion of the pituitary and of the adrenal cortex. The simultaneous reduction of 17-ketosteroid excretion in a debilitated patient is not surprising if the different functions and responses of the three zones of the adrenal cortex are considered.

Increased permeability of the endothelium has been suggested as a cause of several forms of edema. However, we must remember that the concentration of protein in the ascitic fluid in cirrhosis is relatively low. It is in the same general range as that seen in patients with nephrosis and with heart failure, in which changes in permeability are not generally accepted as present. Dr. Kark's thoughts concerning increased permeability should stimulate more detailed study of this possibility.

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33. Sprague, R. G.; Power, M. H.; Mason, H. L.; Albert, A.; Mathieson, D. R.; Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Observations on the Physiologic Effects of Cortisone and ACTH in Man, Arch. Int. Med. **85**:199-258 (Feb.) 1950.

EPILEPSY IN SYSTEMIC LUPUS ERYTHEMATOSUS

Effect of Cortisone and ACTH

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AND
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THE DISCOVERY of the L. E. (lupus erythematosus) phenomenon [1] in vivo [2] and in vitro [3] has provided accurate diagnostic procedures for acute disseminated lupus erythematosus. These tests have given consistently positive reactions in typical cases of lupus. Moreover, they have indicated that the disease may exist for varying lengths of time in previously unrecognized forms before entering into the final, familiar clinical picture. The present study was prompted by the observation of protracted grand mal epileptic attacks in six of 23 lupus patients with positive L. E. test reactions. In brief, it is our contention that any patient with epilepsy and rheumatoid arthritis may have systemic [4] lupus erythematosus.

The association of convulsive seizures with lupus erythematosus has been noted in many case reports, though no specific reference devoted to a correlation of the two entities has been found in the literature. To our knowledge electroencephalographic evidence of cerebral damage in systemic lupus erythematosus has not been presented. Complete neuropathologic studies have been rare. A study of the case reports revealed no instance in which epilepsy occurred as a prodromal symptom for several years.

It seems appropriate, therefore, to report in some detail those cases of systemic lupus erythematosus in which we have observed convulsions, electroencephalographic abnormalities or histopathologic brain changes, and to stress the value of the plasma L. E. test in detecting epilepsy due to lupus long before the terminal stages.

This investigation was supported (in part) by a research grant from the National Institutes of Health, United States Public Health Service.

Dr. Russell was formerly Fellow in Medicine, Cleveland Clinic. His present address is Wichita Clinic, Wichita, Kan. Dr. Haserick and Dr. Zucker are from the Cleveland Clinic and the Frank E. Bunts Educational Institute.

1. The L. E. phenomenon consists of (1) clumping of leukocytes and (2) L. E. cells.

2. Hargraves, M. M.; Richmond, H., and Morton, R.: Presentation of 2 Bone Marrow Elements: "Tart" Cell and "L.E." Cell, Proc. Staff Meet., Mayo Clin. **23**:25 (Jan. 21) 1948.

3. Haserick, J. R., and Bortz, D. W.: (*a*) Normal Bone Marrow Inclusion Phenomenon Induced by Lupus Erythematosus Plasma, J. Invest. Dermat. **13**:47 (Aug.) 1949; (*b*) New Diagnostic Test for Acute Disseminated Lupus Erythematosus, Cleveland Clin. Quart. **16**:158 (July) 1949. (*c*) Haserick, J. R.: Blood Factor in Acute Disseminated Lupus Erythematosus, Arch. Dermat. & Syph. **61**:880 (June) 1950. (*d*) Hargraves, M. M.: Production in Vitro of the L.E. Cell Phenomenon, Proc. Staff Meet., Mayo Clin. **24**:234 (April 27) 1949.

4. The term "systemic" will be used synonymously with "acute or subacute disseminated" lupus erythematosus.

REVIEW OF THE LITERATURE

Sixty-two individual case reports and three case series [5] of systemic lupus erythematosus appearing in the literature since 1935 were reviewed. Among the 144 patients represented, 22 (15 per cent) were reported to have had convulsions. Fifteen patients had seizures only during the terminal phases of the disease.[6] Four patients had isolated grand mal seizures during the active, preterminal phase.[7] For the other three patients the sequence of symptoms was not detailed.[5b] There were no case reports establishing the onset of convulsions prior to the appearance of other systemic symptoms.

Klemperer, Pollack and Baehr [5c] noted terminal convulsions in six of 20 patients. Terminal convulsions were reported in most cases to be accompanied with other toxic cerebral manifestations. Some were coincidental with congestive heart failure,[6c] otitis media and meningitis [6f] and meningioma.[5b] Convulsions during the active, preterminal phase occurred in the absence of uremia [6c] and were sometimes followed by other neurologic manifestations, such as transient amaurosis,[7d] choreiform movements [7c] and, often, terminal cerebral manifestations. Apparently none of the patients reported on in the literature had prolonged anticonvulsant therapy.

Only five cases have been described in which postmortem examinations were done on the brains of patients who had convulsions with lupus erythematosus. In 1943 Pollak and Ziskind [6f] reported on one patient who had experienced repeated terminal seizures, presumably as a symptom of otitis media and meningitis. Autopsy disclosed perivascular degeneration, glial proliferation and cerebral thrombi composed of fibrin and necrotic cells. These cells, which also were seen outside the cerebral vessels, were considered similar to liver cells found within the hepatic vessels as a result of liver damage from sulfonamide. It should be noted, however, that convulsions occurred before the administration of sulfonamide. Lian [6d,e] reported on one

5. (*a*) Coburn, A. F., and Moore, D. H.: Plasma Proteins in Disseminated Lupus Erythematosus, Bull. Johns Hopkins Hosp. **73**:196 (Sept.) 1943. (*b*) Tumulty, P. A., and Harvey, A. M.: Clinical Course of Disseminated Lupus Erythematosus, ibid. **85**:47 (July) 1949. (*c*) Klemperer, P.; Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, Arch. Path. **32**:569 (Oct.) 1949.

6. (*a*) Footnote 5 *a* and *b*. (*b*) Acute Disseminated Lupus Erythematosus, Cabot Case 27301, New England J. Med. **225**:151 (July 24) 1941. (*c*) Guion, C. M., and Adams, E. C.: Six Autopsied Cases of Disseminated Lupus, Am. J. M. Sc. **205**:33 (Jan.) 1943. (*d*) Lian, C.; Siguier, F., and Sarrazin, A.: Les lupo-érythémato-viscérites malignes (élargisement nosographique de la "maladie" de Libman-Sachs), Bull. et mém. Soc. méd. hôp. Paris **63**:167, 1947. (*e*) Lian, C.; Siguier, F.; Duperrat, B., and Sarrazin, A.: Lupo-érythémato-viscérite maligne à évolution fatale malgré une pénicillothérapie massive (obsérvation anatomo-clinique), ibid. **63**:193, 1947. (*f*) Pollak, O., and Ziskind, J. M.: Death During Sulfonamide Treatment, J. Nerv. & Ment. Dis. **98**:648 (Dec.) 1943. (*g*) Vesey, J. M., and Nelson, H. G.: Acute Disseminated Lupus Erythematosus, Ann. Int. Med. **32**:565 (March) 1950. (*h*) Graffin, J. W.; Taylor, C. B., and Hass, G. M.: Clinical and Pathologic Study of Disseminated Lupus Erythematosus, M. Clin. North America **33**:79 (Jan.) 1949. (*i*) Curtis, A. C., and Horne, S. F.: Disseminated Lupus Erythematosus with Pericardial Effusion, Ann. Int. Med. **30**:209 (Jan.) 1949.

7. (*a*) Guion and Adams.[6c] (*b*) Ginzler, A. M., and Fox, T. T.: Disseminated Lupus Erythematosus, Arch. Int. Med. **65**:26 (Jan.) 1940. (*c*) Acute Disseminated Lupus Erythematosus, Cabot Case 27402, New England J. Med. **225**:549 (Oct. 2) 1941. (*d*) Jarcho, S.: Lupus Erythematosus Associated with Visceral Vascular Lesions, Bull. Johns Hopkins Hosp. **59**:262 (Nov.) 1936.

patient with repeated terminal convulsions who at autopsy had large areas of softening in the brain, extreme vascular congestion and cerebral thrombi. One patient with lupus erythematosus described by Tumulty and Harvey [6b] had convulsions coincidental with a meningioma. Another in their series had terminal Jacksonian seizures; autopsy revealed an intracerebral hematoma in the left occipital lobe, in which fibrinoid degeneration was cited as a possible etiologic factor. Vesey and Nelson [6g] recently reported a case of systemic lupus erythematosus in a Negro who had terminal convulsions; histopathologic changes consisting of neuronophagia, chromatolysis and vascular congestion were noted, but there was no evidence of infection, degeneration or infarction.

Eleven case reports of systemic lupus erythematosus in patients without convulsions have included neuropathologic observations. Cortical atrophy, meningeal edema and hydrocephalus have been observed, as well as Gasserian ganglion involvement and infarct of the hippocampus.[8] Jarcho [7d] encountered one patient with encephalomalacia and cerebral thrombosis. Fisher [9] observed a normal brain in a patient who had microscopic cord lesions consistent with acute ascending myelitis from sulfonamide sensitivity. Keil [10] reported chronic meningoencephalitis. Cluxton and Krause [11] described a case with cortical atrophy, perivascular atrophy in the basal ganglions and pontine hemorrhages. Other reports have described additional nonspecific changes, such as hyaline thickening and calcification of the small arteries [12] and petechiae in the brain.[6b] In a careful neuropathologic study Daly emphasized in one case extensive vascular changes and thrombosis associated with nonspecific encephalitis.[13]

REPORT OF CASES

Since February 1949, 28 patients with positive reactions on plasma L. E. tests have been observed at the Cleveland Clinic. Seven of these patients had convulsions. The conditions of two had been diagnosed and treated as idiopathic epilepsy for years before the onset of recognizable lupus symptoms. For the last 11 patients electroencephalograms were recorded routinely. Postmortem examination of the brain was performed on four patients. The cases are classified into three groups according to the chronologic relation between the epileptiform seizures and the other manifestations of lupus erythematosus. One group of patients who experienced no convulsions is described to illustrate pertinent electroencephalographic or neuropathologic data.

8. Montgomery, H.: Disseminate Lupus Erythematosus as a Systemic Disease, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1940, Vol. 4, Part i, Chap. I-C, pp. 44(41)-44(65).

9. Fisher, J. H., and Gilmour, J. R.: Encephalomyelitis Following Administration of Sulphanilamide, Lancet **2**:301 (Aug. 5) 1939.

10. Keil, H.: Dermatomyositis and Systemic Lupus Erythematosus, Arch. Int. Med. **66**: 109 (July) 1940.

11. Cluxton, H. E., and Krause, L. A. M.: Acute Lupus Erythematosus Disseminatus, Ann. Int. Med. **19**:843 (Dec.) 1943.

12. Criep, L. E.: Collagen Disease: Its Relation to Hypersensitiveness, J. Allergy **20**:116 (March) 1949.

13. Daly, D.: Central Nervous System in Acute Disseminated Lupus Erythematosus, J. Nerv. & Ment. Dis. **102**:461 (Nov.) 1945.

Group I: Epilepsy preceding active systemic lupus erythematosus.

CASE 1.—A woman, aged 38, entered the Cleveland Clinic Hospital on Sept. 24, 1949, with convulsions, arthritis and fever. Grand mal seizures had occurred monthly since 1934. Since 1936 she had had arthralgia and a nontuberculous pleural effusion. An electroencephalogram in 1947 had shown slightly abnormal slow waves, predominantly on the left side. In July 1949 she had experienced a persistent febrile exacerbation of arthritis and polyserositis, accompanied with an increase in frequency of convulsions.

Physical examination revealed malar erythema and pigmentation, lymphadenopathy, interphalangeal synovial swelling, a mitral systolic murmur and pretibial edema. Results of neurological examination were normal.

Laboratory examinations disclosed leukopenia, anemia and albuminuria. The plasma L. E. test gave repeatedly positive reactions. A chest roentgenogram demonstrated pleural effusion and left auricular enlargement. Determination of the plasma proteins by the Longsworth modification of the Tiselius electrophoretic technic showed a significant increase in the gamma globulin fraction.

Course and Treatment.—Clinical improvement was noted with twice daily intravenous infusions of 1.5 mg. of epinephrine. Since her hospital discharge on Oct. 25, 1949, the patient has continued to manifest clinical activity of systemic lupus erythematosus, as reflected by consistently

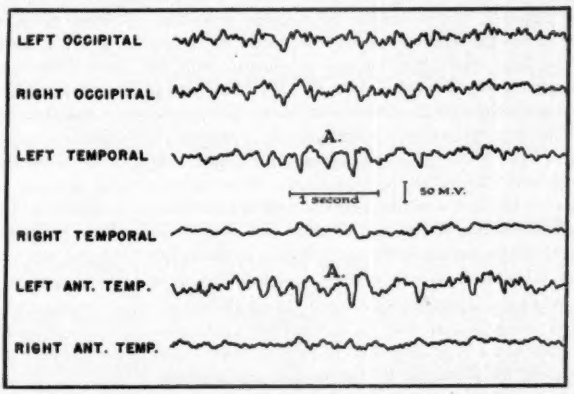

Fig. 1 (case 1).—Electroencephalogram taken April 4, 1950, showing abnormal focal delta activity (*A.*) in the left temporal leads. A later tracing showed progressive abnormality.

positive plasma L. E. test reactions and low grade symptoms. Grand mal seizures have been reduced in frequency; however, memory lapses without loss of consciousness and muscular twitching have appeared for the first time. Between Feb. 4 and March 13, 1950, weekly injections of 60 mg. of testosterone cyclopentylpropionate were given; since March 20, semiweekly injections of 100 mg. of cortisone acetate have been administered, and since June 6, 20 mg. of pituitary adrenocorticotropic hormone (ACTH) twice weekly. There has been a gradual improvement in all symptoms.

An electroencephalogram recorded on April 4, 1950 (fig. 1) showed an abnormal organic focal pattern, with delta waves arising from the left temporal region. While these waves were similar to those recorded from the left side in 1947, they were more abnormal. On June 13, 1950 an electroencephalogram exhibited slightly progressive abnormality from the previous record.

Summary of Case 1.—This patient has had a low grade illness of 14 years' duration, manifesting arthritic, pleuritic, cardiac and cutaneous symptoms of systemic lupus erythematosus. Epileptiform seizures antedated the illness by two years and have fluctuated in frequency in proportion to the severity of her systemic symptoms. Electroencephalograms taken before and after the severest relapse have demonstrated a change to an abnormal organic focal type pattern.

CASE 2.—A woman, aged 32, was admitted to the Cleveland Clinic Hospital on Nov. 18, 1949. In 1932 she had become incapacitated by frequent grand mal and petit mal seizures. Monthly seizures had occurred for several years before November 1948, when she had become acutely ill with arthritis, pleuritic pain, fever and weight loss. In May 1949 a positive reaction to a plasma L. E. test substantiated the diagnosis of systemic lupus erythematosus.

Symptoms and laboratory data indicated progressive involvement of the skeletal, cardiovascular, renal and hemopoietic sytsems; the only cutaneous manifestation was a transient petechial eruption on the mucous membrane. Convulsions continued at monthly intervals despite anticonvulsant therapy, which was discontinued in October 1949.

Course.—Injections of 25 mg. of cortisone acetate were given four times daily between Nov. 22 and Dec. 13, 1949. A pronounced improvement resulted. No seizures occurred while the patient received cortisone. The first convulsions in two months took place one day subsequent to discontinuance of therapy. On December 15 an electroencephalogram showed a normal alpha pattern, which was unaltered after a test injection of 25 mg. of cortisone. On December 19 a temporary relapse was noted, and for the first time the typical malar erythema of lupus erythematosus appeared. After receiving daily injections of testosterone cyclopentylpropionate, she was discharged from the hospital on Jan. 17, 1950.

An ambulatory clinical status has been maintained, with successive courses of treatment with testosterone, cortisone and ACTH, each given weekly or semiweekly, depending on the clinical response. The plasma L. E. test reaction has remained consistently positive. Grand mal seizures have occurred at monthly intervals during this period of clinical activity. The frequency of the convulsions has been diminished, but not eliminated, with the above maintenance therapy. An electroencephalogram recorded on June 13, 1950, seven days after the first injection of 40 mg. of ACTH, showed an abnormal pattern, with some random slow waves and short paroxysms of slow dysrhythmia interspersed with longer periods of normal alpha activity.

Summary of Case 2.—A patient had epilepsy for 16 years prior to the diagnosis of systemic lupus erythematosus. During the past six months of low grade activity of lupus, the frequency of her convulsions has been diminished by low maintenance doses of cortisone or ACTH. Moreover, an electroencephalogram recorded shortly after a remission induced by cortisone therapy was normal, whereas a tracing made six months later showed an abnormal pattern.

Group II: Epilepsy during the active, preterminal phase of systemic lupus erythematosus.

CASE 3.—A woman, aged 28, was critically ill on admission to the Cleveland Clinic Hospital on Oct. 8, 1949. Since January 1948, she had had progressive synovial swelling, lymphadenopathy, weight loss, fever and a facial eruption. In January 1949, a skin biopsy specimen revealed lupus erythematosus and the plasma L. E. test reaction was positive.

Physical examination revealed mucocutaneous lupus erythematosus, lymphadenopathy, a precordial systolic murmur and severe synovial swelling, cellulitis and ecchymoses about the right ankle.

Laboratory Data.—Examination of the blood revealed anemia and leukopenia. The blood urea was 42 mg. per 100 cc. The reaction to the plasma L. E. test remained positive. A roentgenogram of the chest demonstrated bilateral pleuritis. Determination of the plasma proteins by the Longsworth modification of the Tiselius electrophoretic technic showed a significant elevation in the gamma globulin fraction. Examination of the urine by the Addis method disclosed the maximal specific gravity to be 1.008; there were 0.40 Gm. of protein, 1,800,000 erythrocytes, 1,100,000 leukocytes and 112,000 casts per 12 hours. The urea clearance test showed 24 and 29 per cent of normal function.

Course and Treatment.—On Oct. 25, 1949 the patient had her first grand mal seizure. The following day injections of lipo-adrenal cortex were begun. On October 29 mental confusion and acute mania simulating a toxic psychosis appeared. Although injections were stopped temporarily, two convulsions occurred. The patient's renal insufficiency was completely reevaluated and did not appear severe enough to account for the cerebral manifestations, which disappeared on resumption of lipo-adrenal cortex injections.

Cortisone acetate, 100 mg. daily, was administered between November 18 and December 24. By December 17 the patient had no subjective symptoms, and nearly all laboratory data had approached normal limits. A plasma L. E. test reaction was negative for the first time. An electroencephalogram recorded on December 15 (fig. 2) showed a normal alpha pattern, which did not change after a test injection of 25 mg. of cortisone. The plasma L. E. test reaction became positive shortly after hospital discharge on Jan. 25, 1950.

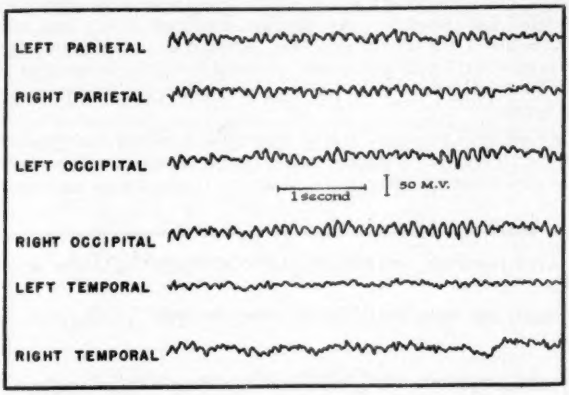

Fig. 2 (case 3).—Electroencephalogram taken Dec. 15, 1949, showing normal waves, 8.5 cycles per second, from occipital and parietal leads.

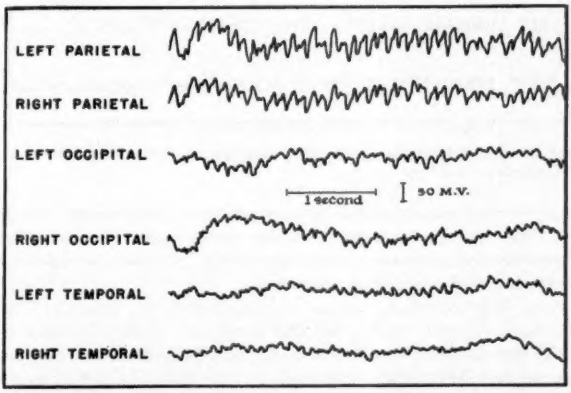

Fig. 3 (case 3).—Electroencephalogram taken March 1, 1950. Comparison with figure 2 shows change to abnormal slow activity predominant in the parietal leads.

Recurrent vomiting and repeated grand mal seizures accompanied a sudden relapse on February 27. On March 1 an electroencephalogram (fig. 3) demonstrated a change from the patient's previous record to a diffuse, abnormal organic record, with the more abnormal waves appearing in the parietal leads. Delta waves of a higher amplitude were recorded from the left side, but there was no evidence of a focal cortical lesion. An electroencephalogram recorded on March 6 (fig. 4) was unchanged in type but showed progressive abnormality.

Cortisone injections were resumed on March 7. Acute mania appeared on March 11, accompanying other terminal manifestations. Convulsions occurred several times daily. When cortisone treatment was discontinued temporarily and anticonvulsant drugs were administered, the psychotic behavior subsided, but convulsions continued at the same frequency. The patient died on March 17, 1950.

Autopsy Observations.—Gross examination of the brain showed nothing unusual, while routine paraffin sections revealed no histopathologic abnormality.

Final pathologic diagnoses included focal basophilic degeneration of the glomeruli of the lupus erythematosus type; focal basophilic degeneration of the lymph nodes; focal necrosis of the adrenal cortex, edema of the adrenal gland and reduction in adrenal cortex lipid material; edema of the myocardium; bronchopneumonia; segmental basophilic degeneration of the aorta; acute splenitis; interstitial edema of the pancreas; reduction of the ova and maturing follicles of the ovaries; ascites.

Summary of Case 3.—A patient had gradual progression of systemic lupus erythematosus over a two year period; convulsions occurred relatively early. Treatment with cortisone induced a symptomatic remission and reversion of the plasma L. E. reaction to negative. During this

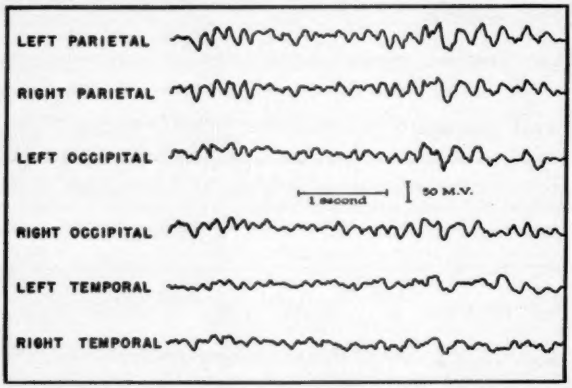

Fig. 4 (case 3).—Electroencephalogram taken March 6, 1950, showing further progression of diffuse low voltage delta activity.

remission, the convulsions ceased and an electroencephalogram was normal. The recurrence of convulsions heralded the patient's terminal relapse, during which two electroencephalograms demonstrated a progressively abnormal organic type change. However, postmortem examination did not reveal changes in the central nervous system.

Case 4.—A 25 year old Negro woman was admitted to the Cleveland Clinic Hospital *in extremis* on April 16, 1949. During her first month of pregnancy in April 1948, she had become acutely ill with fever, edema and an exacerbation of an erythematous, photosensitive facial eruption which had been quiescent for nine years. In July 1948 she had had several grand mal seizures, followed one month later by a spontaneous abortion. Left pleural effusion, weight loss and amenorrhea had been present for six months prior to admission.

Physical examination revealed lupus erythematosus on the face, exudative retinal vasculitis, lymphadenopathy and generalized arthritis. Laboratory determinations established the presence of anemia, leukopenia, hyperglobulinemia and renal insufficiency with azotemia. The plasma L.E. test reaction was positive. Electroencephalography was not performed. The patient died of congestive heart failure on April 26, 1949. Despite severe terminal manifestations of the disease, no convulsions or neurologic signs were observed. Permission for autopsy was not obtained.

Summary of Case 4.—A 25 year old Negro woman experienced systemic lupus erythematosus for one year prior to death. Several grand mal seizures occurred during the second month of her illness.

CASE 5.—A woman, aged 41, was first observed at the Cleveland Clinic on May 2, 1947. In 1938 she had had a short episode of generalized arthralgia, which had recurred in December 1946. The past history revealed a diagnosis of latent syphilis.

Physical examination revealed nothing abnormal except for tenderness of the right knee. Laboratory data included a leukocyte count of 1,900. The Wassermann reaction was negative; the Kahn reaction was 2 +. During the patient's last visit in June 1947, the final diagnoses were osteoarthritis and latent syphilis.

Course.—Shortly thereafter the patient became much worse, and she was admitted to another hospital with arthritis, thrombophlebitis, an erythematous facial eruption and bilateral pleural effusion. During the next two years she had a constant low grade fever and leukopenia. In December 1949 she first experienced grand mal seizures, which occurred frequently despite anticonvulsant therapy. The convulsions ceased spontaneously six weeks later, and no further cerebral manifestations were noted.

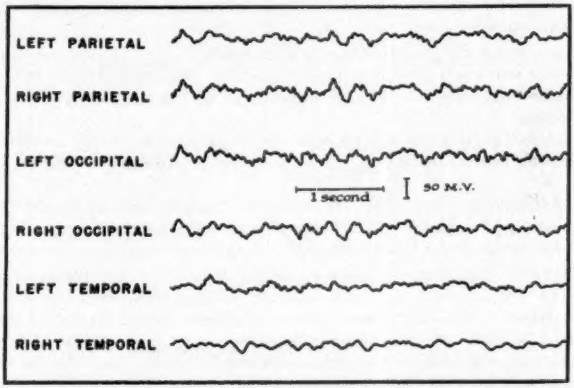

Fig. 5 (case 6).—Electroencephalogram taken Feb. 8, 1950, showing diffuse low voltage delta waves.

On admission to another hospital on March 21, 1950, she was *in extremis* with arthritis, fever, severe diarrhea and peripheral vascular collapse. Pericardial effusion, pleural effusion and hepatosplenomegaly were present. The reaction to a plasma L.E. test was positive. An electroencephalogram recorded on April 10 showed a moderately abnormal record compatible with encephalopathy. With cortisone and ACTH therapy a dramatic remission was effected, and the patient was ambulatory on hospital discharge.

Summary of Case 5.—A patient had a low grade illness of long duration, masquerading as latent syphilis. During an untreated relapse of systemic lupus erythematosus, frequent grand mal seizures occurred for six weeks before ceasing spontaneously. An electroencephalogram later demonstrated a cerebral dysrhythmia.

Group III: Epilepsy during the terminal phase of systemic lupus erythematosus.

CASE 6.—A girl, aged 17, was admitted to the Cleveland Clinic Hospital on Dec. 16, 1949. For two years she had experienced gradual progression of arthritis, fever and weight loss. Previous examinations had established the presence of horseshoe kidney with pyelonephritis.

Physical examination revealed an acutely ill patient with malar erythema, tender cervical lymphadenopathy and an apical systolic murmur.

Laboratory data showed anemia and leukopenia. The reaction to the plasma L.E. test was positive. An Addis examination of the urine showed 2.42 Gm. of protein per 24 hours; three urine cultures were sterile.

Course and Treatment.—By Feb. 3, 1950 the patient was *in extremis* with fever, pleural effusion and cardiac enlargement. The urea clearance tests showed 75 and 65 per cent of normal function. Proteinuria had increased to 11.5 Gm. per 24 hours. The plasma L.E. test gave a positive reaction.

Cortisone acetate was administered between February 4 and 22. Shortly after the first injection, the patient had her first grand mal seizure. Generalized colonic convulsions occurred before breakfast, unrelated to cortisone injection, on February 6 and 7. The fasting blood sugar values on these days were normal. Anticonvulsant therapy did not prevent several additional preprandial convulsions; the last occurred on February 11.

An electroencephalogram recorded on February 8 (fig. 5) showed an abnormal organic type tracing in which higher voltages were noted over the right hemisphere. While the patient had no additional convulsions, on February 12 the following terminal neurological manifestations occurred: neurogenic vesical dysfunction, anisocoria, transient amaurosis, cerebral paraplegia and mental confusion. A lumbar puncture revealed normal findings. The patient died Feb. 22, 1950. Permission for autopsy was not obtained.

Summary of Case 6.—After a two year course of arthritic, renal, pleuritic and cardiac symptoms, convulsions and neurological evidence of cerebral involvement occurred during the terminal phase of this patient's disease. An electroencephalogram showed a dysrhythmia consistent with organic brain disease.

Case 7.—A woman, aged 26, was admitted to the Cleveland Clinic Hospital on Jan. 28, 1949. During a pregnancy four years previously she had had fever and polyarthritis. For one month prior to the present admission, she had been acutely ill with cough, dyspnea, pleuritic pain, orthopnea and edema.

Physical examination revealed hypertension, lymphadenopathy, mitral insufficiency with cardiac enlargement, ascites and edema. The neurological examination revealed a normal condition.

Laboratory determinations established the presence of anemia, leukopenia and renal insufficiency with azotemia. The plasma L.E. test reactions were consistently positive. Roentgenograms of the chest demonstrated pleural effusion. No electroencephalogram was made.

Course.—Additional manifestations appearing during hospitalization included hepatomegaly, anasarca, diarrhea and vomiting, peripheral vascular collapse, pharyngeal ulcerations and a typical malar erythema. Terminally, the patient experienced mental confusion, oliguria and slight azotemia for a 15 day period. During the two days prior to death, she had three grand mal seizures which were unrelated to concurrent treatment. She died on April 10, 1949.

Autopsy Observations.—Gross examination of the brain disclosed no abnormality. Microscopic study of routine paraffin sections showed only diffuse perivascular infiltration and edema. Final pathologic diagnoses included nephritis of the lupus erythematosus type; fibrinous pericarditis and acute focal valvulitis; acute splenitis; acute interstitial pancreatitis; acute fibrinous pleuritis.

Summary of Case 7.—A woman had extensive involvement with systemic lupus erythematosus for four years prior to her death. The terminal phase was accompanied with mild uremia, during which mental confusion and convulsions occurred. Postmortem examination of the brain revealed diffuse perivascular infiltration and edema.

Group IV: Electroencephalographic and neuropathologic abnormalities without convulsions.

Case 8.—A girl, aged 17, was admitted to the Cleveland Clinic Hospital *in extremis* on June 15, 1949. Eleven months prior to admission she had experienced polyarthritis and intermittent fever. One month before admission she had become critically ill with continuous fever, an erythematous facial eruption and pleuritic pain.

Physical examination revealed cutaneous lupus erythematosus on the face, with pharyngeal ulcerations. Lymphadenopathy and generalized synovial swelling were present. The neurological examination disclosed hypoactive reflexes and a cloudy sensorium.

Laboratory examinations demonstrated anemia with a normal leukocyte count, albuminuria and microscopic hematuria. The blood urea was 306 mg. per 100 cc. A roentgenogram of the chest showed a massive pneumonitis of the right lung. The plasma L.E. test gave a positive reaction. No electroencephalogram was made.

The patient became comatose four days after admission and died on June 20, 1949. No convulsions were noted during the course of her illness.

Observations at Autopsy.—Gross examination of the brain revealed no abnormalities. Among routine sections, microscopic study of the right internal capsule showed perivascular hemorrhage in one area and an increase in the perivascular spaces with adventitial thickening. A section through the right pons revealed fibrinoid degeneration of one relatively large vessel.

Other pathologic observations included pulmonary aspergillosis and suppurative bronchopneumonia; verrucous valvulitis and focal necrosis of the mitral valve; nephritis of the lupus erythematosus type.

Summary of Case 8.—A 17 year old girl had systemic lupus erythematosus for 11 months before death; the sole cerebral manifestation was coma during the terminal phase. Postmortem brain examination revealed a perivascular hemorrhage in the internal capsule and fibrinoid degeneration of one pontine vessel.

CASE 9.—A 37 year old woman was transferred to the Cleveland Clinic Hospital on March 20, 1950. Since 1942 she had had chronic discoid lupus erythematosus. In December 1949

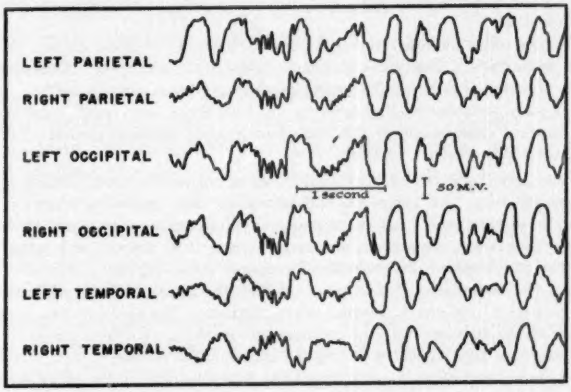

Fig. 6 (case 9).—Electroencephalogram taken March 28, 1950, showing diffuse high voltage delta waves.

she had become acutely ill with fever, weight loss, dyspnea and arthritis. Investigation by the referring physician had revealed a positive plasma L.E. reaction. On admission the patient was *in extremis.*

Physical examination revealed mucocutaneous lupus erythematosus, lymphadenopathy, mitral insufficiency with congestive heart failure and hepatomegaly.

Laboratory data included a leukocyte count of 7,400, with 94 per cent neutrophils. The plasma L.E. test reaction was positive. An Addis examination of the urine showed the maximal specific gravity to be 1.01: there were 0.82 Gm. of protein, 650,000 erythrocytes, 600,000 leukocytes and 450,000 casts per 12 hours. The urea clearance tests showed 98 and 76 per cent of normal function. An adrenal function test showed no eosinophils before or after injection of 25 mg. of ACTH.

A routine electroencephalogram recorded on March 27 (fig. 6) disclosed an abnormal organic type pattern, in which slower frequencies were noted over the right hemisphere. There were no convulsions or other neurological manifestations during the course of her illness. The patient showed no response to treatment with digitalis and 200 mg. of cortisone daily and died on March 30, 1950.

Autopsy Observations.—Gross examination of the brain showed nothing unusual. Microscopic study of paraffin sections obtained from the premotor, motor, parietal and occipital areas revealed scattered clear vacuoles within the white matter. Pyroxylin preparations of sections from the same areas showed similar vacuolation and patches of decreased density of white matter. The relation of the vacuolation to the cell walls was indefinite. Fat stains were not attempted. No vascular abnormalities were observed in the pyroxylin preparations.

Final pathologic diagnoses included lupus erythematosus, myocardial edema, bronchopneumonia, granulocytic hyperplasia and focal lymphocytic infiltration of the bone marrow, edema and necrosis of lymph nodes, ossification of the right adrenal gland and reduction of adrenal cortex lipid material, focal myxomatous change of joint ligaments and adjoining cartilage, ascites and perivascular fibrosis of spleen.

Summary of Case 9.—A 37 year old woman experienced rapidly progressing systemic lupus erythematosus during which no neurological manifestations were noted. An electroencephalogram revealed cerebral dysrhythmia during the terminal phase of her disease. Postmortem examination of the brain disclosed diffuse vacuolation of the white matter.

CASE 10.—A 17 year old girl was admitted to the Cleveland Clinic Hospital on April 13, 1950. One month prior to admission she had become acutely ill with arthritis, pleuritic pain, abdominal pain and extreme weakness. For two weeks prior to admission she had noted fever and a facial eruption.

Physical examination revealed typical lesions of lupus erythematosus on the face, buccal mucosa and finger tips. The cervical lymph nodes were enlarged. A precordial systolic murmur was present. Results of the neurological examination were normal.

Laboratory data established the presence of leukopenia and renal insufficiency without azotemia. Roentgen examination of the chest demonstrated bilateral pleural effusion. Several plasma L.E. tests gave positive reactions.

Course.—Between April 14 and May 3 injections of cortisone acetate totaling 160 to 200 mg. were administered daily. All symptoms and laboratory data showed satisfactory improvement after two weeks of treatment. An electroencephalogram recorded on April 18, before clinical improvement was evident, showed an abnormal pattern with diffuse moderately slow waves.

ACTH was administered in gradually increasing doses beginning May 4. An electroencephalogram recorded during the period of ACTH therapy on May 18, while the patient was in relative remission, showed a normal alpha pattern. The patient has continued to be relatively well on maintenance doses of cortisone given orally. No convulsions or other neurological manifestations have appeared during the course of her illness.

Summary of Case 10.—A 17 year old girl with rapidly progressing systemic lupus erythematosus had a remission induced by ACTH and cortisone therapy. Electroencephalograms taken before and after the remission demonstrated a change from an abnormal to a normal record.

CLINICAL OBSERVATIONS

Among a consecutive series of 28 patients demonstrating positive reactions to plasma L. E. tests at the Cleveland Clinic, 10 patients had one or more of the following central nervous system manifestations: convulsions, cerebral dysrhythmia and histopathologic brain changes.

Epilepsy was the most frequent cerebral manifestation and was encountered in seven patients. It is emphasized that two of these patients had convulsions prior to the recognized activity of systemic lupus erythematosus and continued to experience seizures during the active phase of their disease. Three patients had convulsions during the active, preterminal phase of lupus; one of these patients also had terminal convulsions. Seizures occurring only during the terminal phase of lupus were noted in two patients. Other significant neurological manifestations, such as manic behavior, mental confusion, neurogenic vesical dysfunction, amaurosis and paraplegia, were noted terminally only in the three patients who had terminal convulsions.

Typical grand mal convulsions were observed in six patients, and a history of seizures was obtained in another. Jacksonian seizures were not observed. Two patients (cases 1 and 2) had petit mal seizures shortly after epilepsy began, but not after the diagnosis of systemic lupus erythematosus. In all patients the frequency of convulsions was altered by changes in the clinical status. During the active, preterminal stages in cases 1, 2, 3, 4 and 5, the occurrence of convulsions evidently was related to temporary exacerbations in other clinical symptoms. No relationship was established between convulsions and hypoglycemia. Uremia was excluded in every patient except one (case 7), in whom the etiological relationship of uremia to terminal convulsions was equivocal.

Cortisone acetate was given to five patients who had convulsions. In one patient (case 6) the first convulsion occurred four hours after the first injection of cortisone; however, seizures stopped spontaneously despite continued administration of cortisone. Four of these patients experienced the onset of epilepsy prior to the administration of cortisone. In two patients with convulsions to whom ACTH was given, convulsions occurred prior to its administration and diminished in frequency thereafter. Five patients received diphenylhydantoin (dilantin®) sodium and phenobarbital without appreciable effect; in another patient (case 2) seizures were controlled by treatment with anticonvulsant drugs before the onset of outspoken lupus erythematosus, but not thereafter. Lipo-adrenal cortex therapy seemed to have a temporary anticonvulsant effect in case 3.

ELECTROENCEPHALOGRAPHIC OBSERVATIONS

Electroencephalograms were recorded with six channel Grass equipment, using standard monopolar and bipolar electrodes. Abnormal patterns were detected in seven of 11 consecutive patients with active systemic lupus erythematosus. Electroencephalograms were obtained in five of the seven patients who had convulsions, and in each patient abnormal changes were noted. Records were taken of six patients with systemic lupus erythematosus who had neither convulsions nor other cerebral manifestations; two of these had electroencephalographic abnormalities, and their descriptions are included in the case reports. Normal records were obtained for four patients with positive plasma L. E. test reactions during the active, preterminal phase.

Two types of abnormal electrical alterations were found: (1) abnormal organic records characterized by moderately high voltage activity at a rate of 3 to 7 cycles per second, with delta waves which frequently exhibited disparity between the two sides, and (2) abnormal slow records of medium voltage activity, having a rate of 6 to 8 cycles per second and showing a diffuse pattern often interspersed with long or short runs of normal alpha activity; these less frequently showed delta waves of unequal amplitude bilaterally. No evidence of focal dysrhythmia was observed in either type. The most consistent finding common to these types was a slow, generally diffuse delta activity which invariably showed some disparity between the two sides. In this respect, the electroencephalograms in systemic lupus erythematosus differed from the symmetrical, diffuse slow waves found in idiopathic convulsive disorders and suggested organic brain disease.

There appears to be a correlation between electroencephalographic changes and the phase of lupus during which the recordings are made. All records taken during the terminal phases were abnormal, while those made during the remissions were normal. It is significant that successive changes were evident in each of the four patients from whom more than one record was obtained. Three patients (cases 1, 2 and 3) had progressively abnormal patterns as activity of the disease was prolonged. In case 10 an abnormal slow record taken shortly after the onset of systemic lupus erythematosus was followed by a normal tracing during a remission induced by cortisone therapy. The three patients on whom single abnormal records were made also had changes of a degree compatible with the severity of their clinical manifestations. Although two patients (cases 2 and 10) had normal records while the reactions to the plasma L. E. tests were positive, they showed abnormal tracings at other times; this suggests that a single normal electroencephalogram during active systemic lupus erythematosus is inconclusive.

In patients with rheumatoid arthritis cortisone therapy has been found to produce alterations in the electrical activity of the brain consisting of an increase [14] or a decrease [15] in the frequency of the alpha waves. ACTH administration may cause a reduction in amplitude and frequency of alpha activity.[15] These effects have not been encountered in our patients with systemic lupus erythematosus, six of whom had electroencephalography concurrently with cortisone or ACTH therapy. Test injections of 25 mg. of cortisone acetate were given to four patients while electroencephalograms were being taken, and no electrical alterations were detected.

PATHOLOGIC OBSERVATIONS [16]

Postmortem brain examinations have been performed in four patients with positive plasma L. E. test reactions. Specimens for paraffin mounting and hematoxylin and eosin staining were obtained routinely from the frontal, parietal and occipital lobes, internal capsule, basal ganglions, cerebellum and pituitary gland. In one case sections were prepared with the pyroxylin technic.

In case 3, in which convulsions were present during the course of the disease, no abnormal brain changes were evident despite electroencephalographic evidence of progressive organic brain disease. In case 7 convulsions and uremia were present during the terminal stage, and diffuse cerebrovascular congestion was noted microscopically. The observations in case 8, in which coma constituted the sole terminal neurological manifestation, included perivascular hemorrhage, adventitial thickening, an increase in the perivascular spaces and fibrinoid degeneration in one vessel. Case 9, in which terminal electroencephalographic changes occurred without neurological symptoms, presented diffuse vacuolation of the white matter in microscopic sections prepared by the pyroxylin technic. Gross examination of the brain disclosed no abnormalities in either case.

We do not consider these histopathologic changes specifically indicative of organic brain disease due to lupus erythematosus, as each alteration may accompany a variety of toxic, degenerative or inflammatory states. This impression is gained

14. Boland, E. W., and Headley, N. E.: Effects of Cortisone Acetate on Rheumatoid Arthritis, J.A.M.A. **141**:301 (Oct. 1) 1949.

15. Hoefer, P. F. A., and Glaser, G. H.: Effects of Pituitary Adrenocorticotropic Hormone (ACTH) Therapy, J.A.M.A. **143**:620 (June 17) 1950.

16. Dr. John B. Hazard, Pathologist, Cleveland Clinic, performed these studies.

also from the descriptions of those 16 neuropathologic studies noted in the literature concerning lupus erythematosus. We agree with Daly's statement [13] that studies of the brain in systemic lupus erythematosus have been too incomplete to permit a clear formulation of any typical alteration. It is important to note that his case is the only report of lupus in which several neuropathologic technics were used; however, his major findings would be recognizable in routine paraffin sections. Daly noted that such changes as necrosis, perivascular demyelination and glial proliferation were dependent on the degree of proliferative endarteritis, medial thickening and thrombosis. He concluded that the pathologic picture is one of diffuse nonspecific encephalitis with extensive vascular damage. We failed to corroborate these observations in our patients with positive reactions to plasma L. E. tests, although one patient (case 8) showed slight vascular changes of a different character.

Our experience, combined with the data available in the literature, indicates that routine study of the brain does not disclose changes diagnostic of lupus erythematosus. It is more likely that only highly specialized neuronal studies would reveal a significant microscopic lesion, if such exists in the central nervous system.

COMMENT

This report has concerned those cases of systemic lupus erythematosus in which epileptiform seizures, electroencephalographic abnormalities or histopathologic brain changes have indicated involvement of the central nervous system. Among 28 consecutive patients with positive reactions to plasma L. E. tests, seven (25 per cent) have experienced convulsions. This incidence is significantly greater than that determined from our review of 144 cases gathered from the literature, in which 22 patients (15 per cent) had convulsions. Each of five patients with convulsions who had electroencephalograms showed records of the abnormal organic type. In addition, two patients without cerebral symptoms had electroencephalographic changes, and only four of the 11 patients whose brain waves were studied had normal tracings. In three of four patients autopsy revealed nonspecific neuropathologic changes.

A review of the clinical data presented reveals that instances of symptomatic epilepsy and cerebral dysrhythmia are prone to occur not only during the active phase of systemic lupus erythematosus but also when the patient is in a relatively normal state. The first patient (case 1) presented a history of "idiopathic" epilepsy commencing two years before the onset of prolonged low grade activity of lupus. Another patient (case 2) manifested epilepsy for 16 years prior to the diagnosis of systemic lupus erythematosus.

The fact that systemic lupus erythematosus may smolder for years before fulminating into the active stage is not sufficiently appreciated. Most textbooks and pertinent reviews ignore this point. Its validity has been emphasized in a previous review [8c] of 23 patients with positive reactions to plasma L. E. tests, in whom the duration of symptoms and signs attributable to lupus erythematosus extended to 10 years. For example, false positive reactions to tests for syphilis antedated the onset of clinical systemic lupus erythematosus in four of five patients who had received antisyphilitic treatment during the course of their disease.

The detection of symptomatic epilepsy and cerebral dysrhythmia in lupus erythematosus should be encouraged, for the possibility exists that these manifestations may occasionally be easily recognizable prodromal symptoms. It is frequently true

that the index of clinical suspicion of systemic lupus erythematosus rises in proportion to the number of systems implicated. Thus, demonstration of central nervous system involvement might indicate the presence of lupus in patients presenting syndromes of doubtful or low grade activity in other systems.

There does not appear to be any characteristic electroencephalographic pattern in the seven cases in which abnormal electroencephalograms were obtained. In two of these cases the tracings were normal at one time and abnormal subsequently. In one case with an abnormal record, the tracing later became normal. Most of the records were believed to be of an organic type because of the low voltage, slow activity and because in two of the cases there were findings suggestive of maximum changes in one hemisphere or a focal type of abnormality.

The etiological mechanism of epileptiform seizures in systemic lupus erythematosus is not easily understood. Hypoglycemia was excluded in each case. In cases in which there were preterminal convulsions, uremia was excluded; although uremia was temporally related to the terminal convulsions in one case, the etiological relationship was equivocal. There was no family history of epilepsy in any case. No correlation existed between postmortem findings and convulsive seizures, and one patient with convulsions and progressive dysrhythmia had a normal brain. The plausible conclusion in each case indicates that the central nervous system manifestations were caused by the etiological factor of systemic lupus erythematosus.

SUMMARY

Epilepsy has been the most important, and by far the most frequent, central nervous system manifestation in patients with proved systemic lupus erythematosus. Reports are presented of patients with positive reactions to plasma L. E. tests in whom convulsive disorders or pertinent electroencephalographic and histopathologic brain changes have occurred.

Seven of 28 patients with positive plasma L. E. reactions have had convulsions during the course of the disease. The incidence of this symptom is significantly greater in this series than among cases accumulated from the literature prior to the introduction of the plasma L. E. test.

Two patients have had convulsions for years prior to the appearance of recognizable symptoms of lupus erythematosus. This suggests that epilepsy, when accompanied with rheumatoid arthritis or leukopenia, may constitute a prodromal symptom of systemic lupus erythematosus.

Electroencephalograms frequently demonstrate an organic type of dysrhythmia in patients with or without convulsions in systemic lupus erythematosus. Progressive and regressive changes in the electroencephalogram may parallel relapses or remissions in this disease. The reliability of the electroencephalogram as a diagnostic aid in detecting cerebral involvement with lupus erythematosus bears further investigation.

Routine pathologic studies have failed to reveal specific brain alterations in lupus erythematosus. The use of more elaborate neuropathologic technics should be encouraged in the study of patients with convulsive disorders or cerebral dysrhythmias; until these histopathologic studies are performed, the mechanism and causation of convulsions in systemic lupus erythematosus must remain in doubt.

Cortisone and ACTH treatment produced improvement in epileptiform seizures related to lupus erythematosus.

Progress in Internal Medicine

RECENT ADVANCES IN NUTRITION

Review of the Literature, 1949-1950

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NEW ORLEANS

INVESTIGATION in the field of nutrition in recent years has been directed toward elucidation of the role of essential nutrients in metabolic processes, exploration of nutrient interrelationships and evaluation of the importance of nutrition in diseases which are primarily non-nutritional in origin or in which etiological relationships to nutrition are uncertain. At the same time, search has been continued for additional chemical substances that may be dietary essentials, and specific syndromes of nutritional deficiency have been more accurately delineated.

The tremendous volume of nutrition research prohibits complete review of all recent contributions. Accordingly, attention will be directed to those subjects which appear to be of particular interest and importance to the clinician from either a theoretical or a practical standpoint.

PROTEIN NUTRITION

Protein Requirement and Metabolism.—Protein metabolism has been a field of paramount interest, and several good reviews of current knowledge of this subject have appeared.[1] One of the most outstanding contributions has been the establishment of human amino acid requirements by Rose.[2] On the basis of 152 metabolic balance studies on healthy male graduate students, he has suggested that when the diet furnishes sufficient nitrogen for synthesis of nonessentials the minimum daily need of the eight essential amino acids, in grams, is as follows: *l*-tryptophane 0.25, *l*-phenylalanine 1.10, *l*-lysine 0.80, *l*-threonine 0.50, *l*-valine 0.80, *l*-methionine 1.10, *l*-leucine 1.10 and *l*-isoleucine 0.70. In formulating diets of low amino acid content, Rose recommends that twice these amounts be included to allow for possible variation upward in the requirement of individual subjects. Albanese and co-workers[3] have estimated the requirements of infants for sulfur-containing amino acids.

The availability of amino acids labeled with radioactive nitrogen (N^{15}) and carbon (C^{14}) has stimulated extensive investigation of protein synthesis and

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1. Ravdin, I. S., and Gimbel, N. S.: Protein Metabolism in Surgical Patients, J. A. M. A. **144**:979 (Nov. 18) 1950. Lewis, H. B.: Proteins in Nutrition, Report of Council on Foods and Nutrition, ibid. **138**:207 (Sept. 18) 1948.

2. Rose, W. C.: Amino Acid Requirements of Man, Federation Proc. **8**:546, 1949.

3. Albanese, A. A.; Holt, L. E., Jr.; Davis, V. I.; Snyderman, S. E.; Lein, M., and Smetak, E. M.: The Sulfur Amino Acid Requirement of the Infant, J. Nutrition **37**:511, 1949.

turnover. Schoenheimer, in 1939,[4] using N^{15}-labeled amino acids, demonstrated that a rapid and constant interchange occurs between the amino acids in body protein and the free amino acids. Sprinson and Rittenberg [5] estimated that the time required for half replacement of body protein in man was about 80 days. The rate of replacement of protein nitrogen appeared to be about 1 Gm. per day.

The rate of plasma protein synthesis and degradation has been studied by Kinsell and co-authors,[6] using methionine labeled with radioactive sulfur. Findings suggest that in normal persons plasma proteins are built up and destroyed at a constant rate and that degradation is a relatively slow process; in patients with chronic liver damage the rate of plasma protein formation is diminished; in idiopathic hypoproteinemia the rate of plasma protein catabolism is increased.

McKee and associates,[7] in studies of experimental ascites in dogs, fed lysine labeled with C^{14} to a donor dog from which blood was later removed and the plasma injected, either intraperitoneally or intravenously, into dogs with ascites. A rapid exchange of protein between ascitic fluid and plasma was demonstrated. A general discussion of the constant interchange between tissue and dietary protein and the homeostatic mechanisms which tend to maintain metabolic processes in a state of dynamic equilibrium has been presented recently by Cannon.[8]

Several studies have indicated that all the amino acids needed for formation of the protein molecule must be available at the same time for protein synthesis to occur.[9] If incomplete amino acid mixtures which supplement one another are fed several hours apart, nitrogen retention does not result. Almquist [10] and others have shown that the proportions of indispensable amino acids to each other, for maximum efficiency of utilization, remain relatively constant at various levels of protein intake. It seems likely, therefore, that amino acid imbalance cannot be corrected by feeding more of an imbalanced protein. Thus, the balance of amino acids in the diet becomes another factor requiring consideration. There is some evidence suggesting that the distribution of protein in the three daily meals, as to both quantity and quality, may influence human protein requirements and utilization.[11]

4. Schoenheimer, R.: The Dynamic State of Body Constituents, Harvard University Monographs in Medicine and Public Health, No. 3, Cambridge, Mass., Harvard University Press, 1942.

5. Sprinson, D. B., and Rittenberg, D.: The Rate of Interaction of the Amino Acids of the Diet with the Tissue Proteins, J. Biol. Chem. **180**:715, 1949.

6. Kinsell, L. W.; Margen, S.; Tarver, H.; Frantz, J. M.; Flanagan, E. K.; Hutchin, M. E.; Michaels, G. D., and McCallie, D. P.: Studies in Methionine Metabolism: III. The Fate of Intravenously Administered S^{35}-Labeled-Methionine in Normal Adult Males, in Patients with Chronic Hepatic Disease, "Idiopathic" Hypoproteinemia and Cushing's Syndrome, J. Clin. Invest. **29**:238, 1950.

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8. Cannon, P. R.: The Dynamic Equilibrium, Am. J. Clin. Path. **19**:99, 1949.

9. Geiger, E.: The Role of the Time Factor in Protein Synthesis, Science **111**:594, 1950. Borsook, H.: Protein Turnover and Incorporation of Labeled Amino Acids into Tissue Proteins in Vivo and in Vitro, Physiol. Rev. **30**:206, 1950. Wissler, R. W.; Frazier, L. E., and Slayton, R. E.: Influence of Time of Ingestion of Essential Amino Acids upon Maintenance of Nitrogen Balance, Proc. Soc. Exper. Biol. & Med. **72**:589, 1949.

10. Almquist, H. J.: Amino Acid Balance at Super-Normal Dietary Levels, Proc. Soc. Exper. Biol. & Med. **72**:179, 1949.

11. Leverton, R. M., and Gram, M. R.: Nitrogen Excretion of Women Related to the Distribution of Animal Protein in Daily Meals, J. Nutrition **39**:57, 1949.

Blood Levels and Excretion of Amino Acids.—Numerous studies of the level of amino acids in the blood, and of the excretion of these substances in the urine and feces, have been carried out in normal subjects and in patients with various disease states. Both chromatographic and microbiologic assay methods have been used for amino acid determinations. Seligson [12] has reported a modified microbiologic procedure which is applicable to small volumes of urine and plasma. In normal persons considerable variation in amino acid excretion has been observed.[13] The rates of excretion of individual amino acids have not been directly correlated with the respective amounts taken in food,[14] nor has the pattern of excretion been related to amino acids administered intravenously.[15] In general, the fasting level of amino acids in the plasma does not fluctuate significantly, despite variations in the quantities ingested,[14b] and does not parallel the amounts excreted in the urine.[13]

Both age and sex variations have been noted for plasma amino acid levels.[16] In liver disease Dunn and associates [17] found that excretion of amino acids was abnormal: High values were common in cirrhosis associated with hepatic cellular damage and jaundice and low values in the absence of jaundice or during healing. Kinsell [6] administered large quantities of *dl*-methionine, 9 Gm. daily, to patients with liver disease and observed a significant elevation of the fasting level of *l*-methionine in the plasma as compared with normal subjects. Continuation of this dosage led to toxic manifestations when liver disease was severe.

No demonstrable differences have been noted in the amino acids excreted in urine or feces or in the free amino acids in the plasma between normal subjects and patients with peptic ulcer.[18] In chronic ulcerative colitis free amino acids in the plasma and urinary excretion of amino acids were found to be within the normal range, but the quantities of amino acids in the feces were significantly increased.[19] This increase was attributed to loss of intestinal secretions, exudate and blood. After surgical procedures, no significant differences in amounts or patterns of amino acid excretion were noted in the presence of a negative nitrogen balance.[20]

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12. Seligson, D.; Torghele, J. R., and Anderson, J. A.: An Improved Method for the Determination of Amino Acids in Small Samples of Blood and Urine, J. Lab. & Clin. Med. **35**:640, 1950.

13. Steele, B. F.; Reynolds, M. S., and Baumann, C. A.: Amino Acids in the Blood and Urine of Human Subjects Ingesting Different Amounts of the Same Proteins, J. Nutrition **40**:145, 1950.

14. (*a*) Steele and others.[13] (*b*) Kirsner, J. B.; Sheffner, A. L., and Palmer, W. L.: Studies on Amino Acid Excretion in Man: III. Amino Acid Levels in Plasma and Urine in Normal Men Fed Diets of Varying Protein Content, J. Clin. Invest. **28**:716, 1949.

15. Harper, H. A.: Intravenous Amino Acid Tolerance Studies in Humans, Proc. Soc. Exper. Biol. & Med. **72**:184, 1949.

16. Hofstatter, L.; Ackermann, P. G., and Kountz, W. B.: The Plasma Levels of 9 Free Amino Acids in Old Men and Women, J. Lab. & Clin. Med. **36**:259, 1950.

17. Dunn, M. S.; Akawaie, S.; Yeh, H. L., and Martin, H.: Urinary Excretion of Amino Acids in Liver Disease, J. Clin. Invest. **29**:302, 1950.

18. Kirsner, J. B.; Sheffner, A. L.; Palmer, W. L., and Sterling, K.: Studies on Amino Acid Excretion in Man: IV. Peptic Ulcer, J. Clin. Invest. **29**:869, 1950.

19. Kirsner, J. B.; Sheffner, A. L., and Palmer, W. L.: Studies on Amino Acid Excretion in Man: V. Chronic Ulcerative Colitis and Regional Enteritis, J. Clin. Invest. **29**:874, 1950.

20. Parson, W.; Mayerson, H. S.; White, A. G. C., and Lyons, C.: The Utilization of Amino Acids by Patients Following Surgery, J. Lab. & Clin. Med. **35**:385, 1950.

The amino acid content of fish and meat products has been investigated as a cooperative project by several laboratories.[21]

Protein Depletion and Rehabilitation.—Interest in the subject of protein depletion and rehabilitation was stimulated by problems encountered during World War II. It had been demonstrated that severe tissue injury, such as that from burns, fractures and surgical measures, was followed by a negative nitrogen balance. Protein deficiency was known to be associated with poor wound healing. It was essential to learn the most effective methods of rehabilitation and to develop, if possible, procedures for evaluating the state of protein nutrition.

Studies of starvation edema showed poor correlation between the concentration of serum proteins and the appearance of edema, thus making doubtful the applicability of Starling's hypothesis in this situation.[22] Herrnring [23] noted that serum protein concentrations were at times above normal in patients with severe undernutrition. Lloyd and co-workers [24] reported a qualitative change in serum proteins in famine edema, although the edema was apparently not caused by the decrease in serum protein concentration. They criticized densitometric methods and the equations for converting density to protein concentration. Kingsley and Machella [25] observed differences in serum albumin and globulin determinations by the biuret and total nitrogen methods in various diseases involving liver damage. Jager and associates [26] compared electrophoretic estimations of serum albumin with results of six chemical methods and found best agreement with the saturated magnesium sulfate method and the quantitative precipitin technique.

Taylor and collaborators [27] studied the effect of acute starvation, semistarvation and induced malaria on the electrophoretic pattern of normal young men. They concluded that there are no specific changes characteristic of caloric undernutrition and that there is no valid evidence relating the decrease in albumin and increase in alpha globulin which is observed in many diseases to the protein deficiency of caloric undernutrition that may accompany these diseases. An interesting finding was an increase in the serum albumin fraction after 12 weeks of semistarvation (weight loss, 18 per cent) with a decrease to normal levels after 24 weeks (weight

21. Nielands, J. B.; Sirny, R. J.; Sohljell, I.; Strong, F. M., and Elvehjem, C. A.: The Nutritive Value of Canned Foods: II. Amino Acid Content of Fish and Meat Products, J. Nutrition **39**:187, 1949.

22. Studies of Hunger Edema in Germany, Nutrition Rev. **8**:51, 1950.

23. Herrnring, G.: Die Eiweisswerte im Serum beim Hungerschaden: Eine statistische Betrachtung zur onkotischen Theorie der Ödementstehung, Klin. Wchnschr. **26**:296, 1948.

24. Lloyd, B. B.; Sinclair, H. M., and Tweedie, M. C. K.: Methods for Estimating Total Serum Protein, Biochem. J. **43**:xvii, 1948; Estimations of Serum Protein in Famine Oedema, ibid. **43**:xvii, 1948.

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26. Jager, B. V.; Schwartz, T. B.; Smith, E. L.; Nickerson, M., and Brown, D. M.: Comparative Electrophoretic and Chemical Estimations of Human Serum Albumin: An Evaluation of 6 Methods, J. Lab. & Clin. Med. **35**:76, 1950.

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loss, 24 per cent). It would be interesting to follow the albumin fraction during more prolonged starvation to learn at what point or under what conditions a decrease might occur.

Pearsall and Chanutin [28] conducted electrophoretic, nitrogen and lipid analyses of plasma and plasma fractions of healthy men and of persons with a variety of diseases. In general, alterations in plasma protein patterns were determined by the severity of the disease and appeared to be nonspecific. Electrophoretic analyses of serum proteins in patients with liver disease have been conducted by several groups.[29] Wallis [30] has discussed changes in electrophoretic pattern in rheumatoid arthritis, interpreting findings in terms of inflammation, tissue destruction and immunization.

The serum protein concentration in normal infants has been reported by Poyner-Wall.[31] Smith [32] found the total serum protein concentration low in premature infants, while the concentration of albumin was not greatly reduced. Administration of human serum albumin intravenously raised the serum protein concentration only temporarily, with a return to the previous level in the course of two to three weeks.

Hollander and associates [33] measured thiocyanate space and total body water, using deuterium oxide as a tracer, in subjects depleted of protein and concluded that the disturbance of water metabolism included the intracellular as well as the extracellular compartment. Harroun and co-authors [34] have suggested a method for estimating extravascular reserves of protein (in interstitial fluid and lymph) by determining the response to the rapid infusion of 1 liter of isotonic sodium chloride solution. Normal persons showed an increase in plasma volume and an increase in total circulating protein; malnourished patients showed a smaller increase in plasma volume and a decrease in total circulating protein. Failure of plasma protein to increase was interpreted as a manifestation of depleted tissue stores.

It is obvious that there is a great need for methods of evaluating protein nutrition and that the usual laboratory procedures are not satisfactory. Reliance must be placed largely on clinical evaluation in conjunction with knowledge of conditions etiologically associated with protein deficiency.

28. Pearsall, H. R., and Chanutin, A.: I. Electrophoretic, Nitrogen and Lipide Analyses of Plasma and Plasma Fractions of Healthy Young Men, Am. J. Med. **7**:297, 1949; II. Electrophoretic, Nitrogen and Lipide Analyses of Plasma and Plasma Fractions in Disease, ibid. **7**: 301, 1949.

29. Ricketts, W. E., and Sterling, K.: Electrophoretic Studies of the Serum Proteins in Virus Hepatitis, J. Clin. Invest. **28**:1477, 1949. Sterling, K., and Ricketts, W. E.: Electrophoretic Studies of the Serum Proteins in Biliary Cirrhosis, ibid. **28**:1469, 1949. Kunkel, H. G., and Ahrens, E. H., Jr.: The Relationship Between Serum Lipids and the Electrophoretic Pattern with Particular Reference to Patients with Primary Biliary Cirrhosis, ibid. **28**:1575, 1949. Kunkel, H. G., and Labby, D. H.: Chronic Liver Disease Following Infectious Hepatitis: II. Cirrhosis of the Liver, Ann. Int. Med. **32**:433, 1950.

30. Wallis, A. D.: The Serum Proteins in Rheumatoid Arthritis, Ann. Int. Med. **32**:63, 1950.

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32. Smith, C. A.; Phillips, K. G., and Roth, R. O.: Effects and Fate of Human Serum Albumin Administered Intravenously and Orally to Premature Infants, J. Clin. Invest. **29**:218, 1950.

33. Hollander, V.; Chang, P., and Co Tui: Deuterium Oxide Thiocyanate Spaces in Protein Depletion, J. Lab. & Clin. Med. **34**:680, 1949.

34. Harroun, J. E.; Levey, S., and Smyth, C. J.: A Method of Evaluating Tissue Protein Stores, Am. J. Med. **7**:410, 1949.

Therapy with Amino Acids and Protein.—Protein hydrolysates and mixtures of pure amino acids have been used in therapy of a wide variety of conditions. Excellent reviews on several aspects of this subject have appeared.[35] It has been demonstrated that protein requirements can be satisfied and nitrogen equilibrium maintained by intravenous administration of properly prepared hydrolysates or amino acid mixtures. It is not possible, however, to make good the requirements of the protein-depleted organism solely by parenteral feeding. Intravenous therapy is not superior to oral feeding, and, in fact, utilization is often less efficient, particularly when infusions are given rapidly. Supplementation of protein hydrolysates with large amounts of individual amino acids may produce an imbalance which can cause a loss of body nitrogen. There is little evidence to support the use of protein hydrolysates orally except, perhaps, in some allergic states or in severe pancreatic deficiency. Pure amino acids lack certain peptides which may be necessary for the maintenance of normal nutrition.

It is often difficult to meet caloric requirements by parenteral therapy. Furthermore, it has been shown that with a constant protein intake nitrogen retention is increased as caloric intake rises.[36] Rice and associates [37] have suggested the addition of alcohol to mixtures of amino acid and dextrose to provide additional calories. Approximately 15 cc. of 78 per cent alcohol per hour in fluids given parenterally is suggested as a practical rate of administration for adults. Another method of providing additional calories is the intravenous use of fat emulsions. Evidence is accumulating concerning the suitability of such preparations for human therapy.[38] Nausea and vomiting following the administration of various amino acid preparations have been found to parallel the free glutamic acid content of the mixture.[39]

Amino acid mixtures have been used in the treatment of peptic ulcer. The findings of Sharick and Campbell,[40] that free and total gastric acidity increases after the intravenous administration of amino acids, may contraindicate such therapy.

Although parenteral administration of nutrients is of great importance, unquestionably oral feeding is much to be preferred whenever possible.

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39. Levey, S.; Harroun, J. E., and Smyth, C. J.: Serum Glutamic Acid Levels and the Occurrence of Nausea and Vomiting After the Intravenous Administration of Amino Acid Mixtures, J. Lab. & Clin. Med. **34**:1238, 1949.

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Human serum albumin has been used in the treatment of a number of hypoproteinemic states. Albumin can be metabolized by normal persons, undernourished subjects and patients with liver disease, when given either orally or intravenously.[41] Hydrolyzed human serum albumin, supplemented with *l*-tryptophane, has been found to be nutritionally adequate and to be metabolized in a manner similar to that of other protein hydrolysates. Proteinuria, which may follow the intravenous administration of albumin, may be due to a physiological response when the maximal absorptive capacity of the renal tubules for protein is exceeded, rather than to renal damage. The picture of congestive heart failure may be produced when albumin is given daily in sufficient amounts to normal subjects.[42] The limitations of therapy with salt-poor human albumin in cirrhosis of the liver were discussed by Faloon.[43] Such therapy may be dangerous in the presence of heart disease or esophageal varices.

A recent finding of practical importance is that plasma from outdated blood can be used for obtaining satisfactory preparations of albumin and of gamma globulin and that immune serum globulin so prepared retains its potency.[44]

Zimmerman and Burgemeister [45] reported that the administration of glutamic acid was effective in raising borderline and high grade defective intelligence quotients. Kerr [46] and Ellson [47] and their colleagues have failed to corroborate these findings.

Kwashiorkor.—Kwashiorkor, or malignant malnutrition, is a syndrome commonly observed in children in certain areas of the world, the etiological basis for which remains undetermined. The syndrome consists of impairment of growth, mental irritability, edema, lowered concentration of plasma albumin, bulky, loose stools containing all types of undigested food, brown, soft, scanty hair, anemia and

41. Smith and others.[32] Waterhouse, C.; Bassett, S. H., and Holler, J. W.: Metabolic Studies on Protein-Depleted Patients Receiving a Large Part of Their Nitrogen Intake from Human Serum Albumin Administered Intravenously, J. Clin. Invest. **28**:245, 1949. Eckhardt, R. D., and Davidson, C. S.: The Nutritive Value of Intravenously Administered Hydrolyzed Human Serum Albumin in Man. J. Lab. & Clin. Med. **34**:1133, 1949. Parson, W.; Mayerson, H. S.; White, A. G. C.; Nieset, R. T., and Lyons, C.: Metabolic Changes Associated with the Administration of Salt-Poor Human Serum Albumin in 2 Cases of Infectious Hepatitis, J. Clin. Invest. **29**:381, 1950.

42. Gimbel, N. S.; Riegel, C., and Glenn, W. W. L.: Metabolic and Cardiovascular Studies of Prolonged Intravenous Administration of Human Serum Albumin, J. Clin. Invest. **29**:998, 1950.

43. Faloon, W. W.; Eckhardt, R. D.; Murphy, T. L.; Cooper, A. M., and Davidson, C. S.: An Evaluation of Human Serum Albumin in the Treatment of Cirrhosis of the Liver, J. Clin. Invest. **28**:583, 1949.

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45. Zimmerman, F. T., and Burgemeister, B. B.: The Effect of Glutamic Acid on Borderline and High-Grade Defective Intelligence, New York J. Med. **50**:693, 1950.

46. Kerr, W. J., Jr., and Szurek, S. A.: Effect of Glutamic Acid on Mental Function-Pilot Study, Pediatrics **5**:645, 1950.

47. Ellson, D. G.; Fuller, P. R., and Urmston, R.: The Influence of Glutamic Acid on Test Performance, Science **112**:248, 1950.

a characteristic dermatitis often termed "crazy pavement dermatosis."[48a] Fatty liver is usually present, and if the condition persists cirrhosis develops. Atrophy of the acinar cells of the pancreas is a fairly constant finding at autopsy.[48] Trowell,[48b] who has had large experience with the disease in Africa, reviewed the subject and pointed out that the most significant dietary defect appears to be a shortage of first class protein of animal origin. The anemia, which may be macrocytic or microcytic, is not associated with a megaloblastic bone marrow and does not respond to folic acid therapy.

Nutrition in Liver Disease.—The importance of protein, carbohydrate and certain other nutrients in the prevention and treatment of liver disease is generally recognized. Liver biopsy has been used recently by a number of investigators in the study of hepatic disease from the standpoints of diagnosis, prognosis and evaluation of therapy.[49] Relationships between results of liver function tests and histological changes have also been investigated.[50] Eckhardt and colleagues[51] have recently studied the effect of protein starvation and protein feeding in subjects with active fatty alcoholic cirrhosis. Improvement in clinical status and liver function occurred when the diet was grossly deficient in protein, in spite of a negative nitrogen balance, but there was little change in histological characteristics of the liver. Choline administration caused a moderate reduction in liver fat. When adequate exogenous protein was provided, morphologic improvement occurred with a decrease in liver fat, a decided increase in protein and a return of cell size and appearance to normal.

Gertzen,[52] in a study of nearly 300 cases of acute hepatitis, found that with a balanced basic diet containing 80 Gm. of protein, 90 Gm. of fat and 320 Gm. of carbohydrate, the course of the illness was uninfluenced, irrespective of whether protein, carbohydrate or fat furnished the remainder of the 3,000 calories in the diet. Strom[53] reported that supplementation of a good diet with methionine had only slight beneficial effects as compared with an unsupplemented diet. Cayer and Cornatzer[54] demonstrated an increase in phospholipid turnover in the plasma of

48. (*a*) Kwashiorkor, Nutrition Rev. **8**:55, 1950. (*b*) Trowell, H. C.: Problems Raised by Kwashiorkor, ibid. **8**:161, 1950.

49. (*a*) Klatskin, G., and Yesner, R.: Factors in the Treatment of Laennec's Cirrhosis: I. Clinical and Histological Changes Observed During a Control Period of Bed-Rest, Alcohol Withdrawal and a Minimal Basic Diet, J. Clin. Invest. **28**:723, 1949. (*b*) Meneghello, J.; Espinoza, J., and Coronel, L.: Value of Biopsy of the Liver in Nutritional Dystrophy: Evaluation of Treatment with Choline and Dried Stomach, Am. J. Dis. Child. **78**:141 (Aug.) 1949. (*c*) Davis, W. D., Jr.: Cirrhosis of the Liver: Serial Biopsy Studies, South. M. J. **42**:828, 1949. (*d*) Davis, W. D., Jr., and Laurens, H., Jr.: Correlation of Results of Liver Function Tests and Liver Biopsy in Hepatic Disease, ibid. **43**:217, 1950.

50. Davis and Laurens.[49d] Liver Function and Liver Structure, editorial, J. A. M. A. **142**:1297 (April 22) 1950.

51. Eckhardt, R. D.; Zamcheck, N.; Sidman, R. L.; Gabuzda, G. J., Jr., and Davidson, C. S.: Effect of Protein Starvation and of Protein Feeding on the Clinical Course, Liver Function and Liver Histochemistry of 3 Patients with Active Fatty Alcoholic Cirrhosis, J. Clin. Invest. **29**:227, 1950.

52. Gertzen, O.: Diet in Treatment of Acute Hepatitis, Brit. M. J. **1**:1166, 1950.

53. Strom, J.: Methionine in Treatment of Acute Hepatitis, Brit. M. J. **1**:1168, 1950.

54. Cayer, D., and Cornatzer, W. E.: The Effects of Lipotropic Substances in the Phospholipide Synthesis in Patients With and Without Chronic Hepatitis as Measured by Radioactive Phosphorus, South. M. J. **42**:669, 1949.

untreated patients with chronic hepatitis following a large dose of choline or methionine. This effect was not noted after a period of treatment or after small daily doses of lipotropic factors. The clinical and metabolic effects of several types of nutrient therapy were evaluated by Morey and co-workers.[55] Improvement of active liver cirrhosis was obtained by Eckhardt and collaborators [56] in patients maintained with amino acids given intravenously as the sole source of protein and lipotropic substances. Effects of therapy on sodium excretion have been studied by Faloon and associates.[57]

Ralli and co-workers [58] compared the course of cirrhosis in patients treated in the conventional manner with the course of those given large amounts of liver extract intravenously as additional therapy. The survival rate after three and five years was considerably higher in the group which had received liver extract. Recent studies in animals suggest a possible explanation for these findings. Experiments conducted in rats and chicks indicate that vitamin B_{12} may play a role in the metabolism of methionine and choline.[59] Among other findings vitamin B_{12} was shown to have a lipotropic effect in rats maintained on a high fat diet or on a low protein, low fat regimen. It has been demonstrated in many earlier studies that methionine, choline plus cystine, liver extract and yeast exert a preventive effect in experimental dietary cirrhosis and are of some therapeutic value.[59a]

The importance of "labile" methyl groups in metabolism has stimulated wide investigation. In a recent review of this subject a relationship of both vitamin B_{12} and folic acid to methyl metabolism [60] was pointed out. Schaefer and associates [61] have been able to show that the nutritional requirements for folic acid, vitamin B_{12} and choline are mutually interdependent in chicks and rats under certain experimental conditions. It seems likely that vitamin B_{12} and folic acid will be found to be related to methionine and choline metabolism in man and that these substances may be found useful in the prevention and treatment of liver injury.

Massive necrosis of the liver has been produced in rats by feeding diets low in protein and deficient in the sulfur-containing amino acids, methionine and cystine. Some observers have failed in attempts to produce necrosis with this type of ration.

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55. Morey, G. R.; Poynter, C. R.; Consolazio, C. F.; Maloney, M. A.; Vorhaus, L. J.; Breimyer, M., and Kark, R. M.: Clinical and Metabolic Effects of Different Nutrients in Patients with Cirrhosis, Am. J. Med. **7**:408, 1949.

56. Eckhardt, R. D.; Faloon, W. W., and Davidson, C. S.: Improvement of Active Liver Cirrhosis in Patients Maintained with Amino Acids Intravenously as the Source of Protein and Lipotropic Substances, J. Clin. Invest. **28**:603, 1949.

57. Faloon, W. W.; Eckhardt, R. D.; Cooper, A. M., and Davidson, C. S.: The Effect of Human Serum Albumin, Mercurial Diuretics and a Low Sodium Diet on Sodium Excretion in Patients with Cirrhosis of the Liver, J. Clin. Invest. **28**:595, 1949.

58. Ralli, E. P.; Leslie, S. H.; Stueck, G. H., Jr.; Shorr, H. E.; Robson, J. S.; Clarke, D. H., and Laken, B.: The Course of Cirrhosis of the Liver in Patients Treated with Large Doses of Liver Extract Intravenously, Medicine **28**:301, 1949.

59. (*a*) Role of Vitamin B_{12} in Metabolism of Methionine, Nutrition Rev. **8**:301, 1950. (*b*) Vitamin B_{12}, Folic Acid, and Choline Interrelations, ibid. **8**:145, 1950.

60. Biochemistry of the Methyl Group, Nutrition Rev. **8**:269, 1950.

61. Schaefer A. E.; Salmon, W. D.; Strength, D. R., and Copeland, D. H.: Interrelationship of Folacin, Vitamin B_{12} and Choline: Effect on Hemorrhagic Kidney Syndrome in the Rat and on Growth of the Chick, J. Nutrition **40**:95, 1950.

Abell and Beveridge [62] presented findings suggesting that any procedure which will inhibit the action of tocopherols will augment the capacity of the diet to produce necrosis.

NUTRITION IN HYPERTENSION

The nutritional aspects of hypertension have received increased attention since 1944, when Kempner [63] reported beneficial effects from the use of a rice and fruit diet. Peschel [64] has recently shown that nitrogen balance can be maintained on the rice diet. Ucko [65] reported experiments with a rice diet, a barley diet and a low sodium regimen and suggested that the main effect of Kempner's diet was due to the low sodium content. Two reviews on the subject of the dietary treatment of hypertension have been published recently.[66] Both of these indicate the need for further study under more controlled conditions. Findings may be summarized as follows: Diets proposed by Allen [67] and by Kempner [68] are low in salt and produce a decrease in the blood pressure in some patients with hypertension, especially of the benign type. Available evidence suggests, but does not prove, that the hypotensive effects are due to restriction of the sodium ion. It is still uncertain whether restriction of salt without a change in total caloric intake is capable of lowering blood pressure. Starvation, semistarvation and reduction of weight in the obese tend to lower blood pressure. Reduction of protein, fat, including cholesterol, or other dietary factors does not have a hypotensive effect.[69]

Handler [70] has discussed the importance of dietary protein, calories and salt in experimental renal hypertension.

FAT NUTRITION

Adipose tissue is often incorrectly considered to be relatively inert. There is abundant evidence for a number of active metabolic functions relative to fat deposition and mobilization and of reticuloendothelial nature.[71] Although the optimal level of fat in the diet is not known, animal experiments suggest that the quantity depends in part on the source of dietary fat.[72] In premature infants, Morales and co-workers [73] have shown that emulsified fat is more readily absorbed than the

62. Abell, R. M., and Beveridge, J. M. R.: The Production of Acute Massive Hepatic Necrosis in Rats by Dietary Means, Canad. J. Research, Sect. E **27**:316, 1949.

63. Kempner, W.: Treatment of Kidney Disease and Hypertensive Vascular Disease with Rice Diet, North Carolina M. J. **5**:125, 1944.

64. Peschel, E., and Peschel, R. L.: Nitrogen Balance on the Rice Diet, J. Clin. Invest. **29**:455, 1950.

65. Ucko, H.: Dietary Treatment of Hypertension, Brit. M. J. **2**:144, 1950.

66. (*a*) Chapman, C. B., and Gibbons, T. B.: The Diet and Hypertension: A Review, Medicine **29**:29, 1950. (*b*) Kahn, S. C., and Stare, F. J.: Nutrition in Medicine, Ann. Rev. Med. **1**:127, 1950.

67. Allen, F. M.: Hypertension and Nutrition, Nutrition Rev. **7**:257, 1949.

68. Kempner, W.: Treatment of Hypertensive Vascular Disease with Rice Diet, Am. J. Med. **4**:545, 1948.

69. Diet and Hypertension, Nutrition Rev. **8**:304, 1950.

70. Handler, P., and Bernheim, F.: Importance of Dietary Protein, Calories and Salt in Experimental Renal Hypertension, Am. J. Physiol. **160**:31, 1950.

71. The Versatility of Adipose Tissue, editorial, Ann. Int. Med. **32**:162, 1950.

72. Desirable Fat Levels in the Diet, Nutrition Rev. **8**:232, 1950.

73. Morales, S. M.; Chung, A. W.; Lewis, J., and Holt, L. E., Jr.: Studies on Fat and Vitamin A Absorption in Premature Infants, Am. J. Dis. Child. **80**:508 (Sept.) 1950.

unemulsified product and that administration of polysorbates (tweens®) appears to improve absorption of fat to some extent. Defective fat absorption has been found to occur in patients after vagotomy.[74] Recent experiments in rats with labeled carbon support the concept that absorbed fat travels largely via lymph channels, although some lipid reaches the blood by another route.[75] A simplified method for determining fecal fat and fatty acids has been suggested by Zuckerman and co-authors.[76]

Fat and Arteriosclerosis.—The role of fat in the genesis of human arteriosclerosis has been the subject of much investigation. Recent work suggests that causative factors may include the plasma concentration of cholesterol and other lipids, the number and size of chylomicrons in the plasma, a tissue factor, such as chondroitin sulfuric acid or other carbohydrate sulfate esters in the arterial intima, and the blood pressure.[77] Several reviews dealing with the etiology of arteriosclerosis have appeared,[78] and relationships to cholesterol metabolism have been discussed.[79] The level of serum cholesterol in "normal" men has not been found significantly related to cholesterol intake over a range of 250 to 800 mg. per day.[80] Although it is possible to lower serum cholesterol if a fat-free diet is administered,[81] Messinger and co-authors [82] showed that feeding of egg yolk powder was followed by an increase in serum cholesterol, whereas feeding cholesterol itself produced no change in serum levels. Extremely interesting data were reported by Gofman and his co-workers [83] with ultracentrifuge techniques. They found that it is not total plasma cholesterol which correlates with vascular sclerosis but the presence and quantity of a particular cholesterol-containing lipoprotein. Preliminary data suggest that dietary restriction of cholesterol may reduce the amount of this lipoprotein. Until more data are obtained, rigid restriction of the intake of cholesterol-containing foods does not seem warranted. There is, however, considerable evidence indicating the importance

74. Fox, H. J., and Grimson, K. S.: Defective Fat Absorption Following Vagotomy, J. Lab. & Clin. Med. **35**:362, 1950.

75. Bloom, B.; Chaikoff, I. L.; Reinhardt, W. O.; Entenman, C., and Dauben, W. G.: The Quantitative Significance of the Lymphatic Pathway in Transport of Absorbed Fatty Acids, J. Biol. Chem. **184**:1, 1950.

76. Zuckerman, J. L.; Zymaris, M. C., and Natelson, S.: A Simple Method for the Determination of Fecal Fat and Fatty Acids, J. Lab. & Clin. Med. **34**:282, 1949.

77. Experimental Studies on Etiology of Atherosclerosis, editorial, J. A. M. A. **143**:1344 (Aug. 12) 1950.

78. Dock, W.: The Causes of Arteriosclerosis, Bull. New York Acad. Med. **26**:182, 1950. Waife, S. O.: Recent Advances in the Study of Arteriosclerosis, Ann. Int. Med. **30**:635, 1949.

79. Katz, L. N.; Stamler, J., and Horlick, L.: Cholesterol Metabolism in Health and Disease: Its Relationship to Arteriosclerosis, Am. Pract. **1**:461, 1950. Cholesterol Metabolism and Arteriosclerosis, Combined Staff Clinics, Am. J. Med. **6**:103, 1949. Steiner, A.: Cholesterol in Arteriosclerosis, with Special Reference to Coronary Arteriosclerosis, M. Clin. North America **34**:673, 1950.

80. Keys, A.: The Relation in Man Between Cholesterol Levels in the Diet and in the Blood, Science **112**:79, 1950.

81. Mellinkoff, S. M.; Machella, T. E., and Reinhold, J. G.: The Effect of a Fat-Free Diet in Causing Low Serum Cholesterol, Am. J. M. Sc. **220**:203, 1950.

82. Messinger, W. J.; Porosowska, Y., and Steele, J. M.: Effect of Feeding Egg Yolk and Cholesterol on Serum Cholesterol Levels, Arch. Int. Med. **86**:189 (Aug.) 1950.

83. Gofman, J. W.; Lindgren, F.; Elliott, H.; Mantz, W.; Hewitt, J.; Strisower, B., and Herring, V.: The Role of Lipids and Lipoproteins in Atherosclerosis, Science **111**:166, 1950.

of the control of obesity as a measure in the prevention of vascular disease.[84] The use of lipotropic agents also appears worthy of trial. Choline has been shown to have protective and curative properties in the experimental arteriosclerosis produced in rabbits by cholesterol feeding.[79] Morrison and Gonzales [85] have reported that administration of large doses of choline significantly reduced the mortality rate due to recurrent coronary thrombosis in a series of 115 patients with coronary arteriosclerosis.

Moreton [86] has suggested that in normal persons with normal plasma lipid levels the development of arteriosclerosis may be attributed to the large particle size of recently absorbed lipids, chylomicrons, which appear after a fat rich meal. Individual subjects were found to differ in the height and duration of chylomicronemia following a fat meal. The hypothesis is that large lipid particles are entrapped in the intima and stimulate phagocytosis by macrophages with the formation of "foam" cells. Neutral fat and fatty acids are absorbed, while the less soluble cholesterol residue remains, forming arteriosclerotic lesions.[77] Becker and associates [87] found hyperchylomicronemia to be commoner in persons of older age groups. They also observed that administration of lipase or of detergents with a fat meal reduced chylomicron counts, and the duration of increased counts, in older subjects to levels observed in younger persons. Zinn and Griffith [88] found a suggestive relationship between the proportion of large fat particles in the serum and atheromatous disease in a small group of patients.

Conn and co-workers [89] have presented evidence which suggests that serum cholesterol may be a precursor of adrenal cortex hormones.

VITAMIN NUTRITION

Vitamin A.—Deficiencies of the fat-soluble vitamins have been reviewed by Youmans.[90] An excellent experimental study of vitamin A deprivation in man has been reported by the Vitamin A Subcommittee of the Medical Research Council of Great Britain.[91] Sixteen subjects received a diet containing about 70 international units of carotene and negligible amounts of vitamin A for 11½ to 25 months. Only three subjects displayed unmistakable signs of deficiency. In all

84. Prevention and Treatment of Atherosclerosis, editorial, J. A. M. A. **141**:392 (Oct. 8) 1949.

85. Morrison, L. M., and Gonzales, W. F.: Effect of Choline as a Lipotropic Agent in the Treatment of Human Coronary Atherosclerosis, Proc. Soc. Exper. Biol. & Med. **73**:37, 1950.

86. Moreton, J. R.: Chylomicronemia, Fat Tolerance and Atherosclerosis, J. Lab. & Clin. Med. **35**:373, 1950.

87. Becker, G. H.; Meyer, J., and Necheles, H.: Fat Absorption and Atherosclerosis, Science **110**:529, 1949.

88. Zinn, W. J., and Griffith, G. C.: Number and Size of Fat Globules (Lipomicrons) in the Circulating Blood in Normal Individuals and in Patients with Coronary Disease, Am. J. Med. **8**:525, 1950.

89. Conn, J. W.; Vogel, W. C.; Lewis, L. H., and Fajans, S. S.: Serum Cholesterol: A Possible Precursor of Adrenal Cortical Hormones, J. Lab. & Clin. Med. **35**:504, 1950.

90. Youmans, J. B.: Deficiencies of the Fat-Soluble Vitamins, report of Council on Foods and Nutrition, J. A. M. A. **144**:34 (Sept. 2) 1950.

91. Hume, E. M., and Krebs, H. A.: Vitamin A Requirement of Human Adults: An Experimental Study of Vitamin A Deprivation in Man, Medical Research Council Special Report Series 264, London, His Majesty's Stationery Office, 1949.

subjects the carotenoid content of the blood fell within three months from an initial average value of 150 international units per 100 ml. to a stable level of 12 to 40 international units. The normal level of plasma vitamin A was taken to be 120 international units per 100 ml. After eight months this value began to decline in 10 subjects, and in four subjects it fell below 50 units after many months. Three of these subjects showed deterioration of dark adaptation a few weeks after this low level of plasma vitamin A was attained, at 10, 12 and 20 months, respectively. Each subject showed a large rise in the final rod threshold and in the time of transition from cone to rod vision. No other signs of depletion occurred in these or any of the other subjects. On the basis of prophylactic and therapeutic tests with vitamin A and carotene, it was concluded that the minimum protective dose of vitamin A was about 1,300 international units daily and of carotene 1,500 international units daily. Approximately twice these amounts was recommended as an estimate of requirement to cover individual variations and to provide a margin of safety. The carotene requirement is given in terms of the "maximum effective dose," meaning the part of a given dose of carotene which is not excreted in the feces. The fecal loss is large and variable, and it is suggested that the requirement in terms of carotene intake is about three times that of vitamin A, or about 7,500 units daily. Other investigators have shown that the availability of carotene from different dietary sources varies widely. Callison and collaborators [92] found that the vitamin A value determined by the rat growth bioassay method ranged from 34 to 67 per cent of the value obtained by chemical analysis in several vegetables tested. Tables of food composition may need revision to include a factor of biologic availability.

There is considerable evidence that vitamin A affects bone growth. Fell and Mellanby [93] have shown that the effect of vitamin A is a direct one by demonstrating changes in cartilage matrix and bone tissue in cultures of fetal bone grown in vitro in solutions of vitamin A.

Congenital malformations involving the eyes, genitourinary tract and cardiovascular system have been induced in fetal and newborn rats by maternal vitamin A deficiency, confirming Warkany's previous studies.[94] Many of the cardiovascular anomalies closely simulate malformations observed in man.[95]

Glover and Morton [96] have postulated that vitamin A may be stored in the liver in two sites, the Kupffer cells and the true storage cells, and that only the vitamin A in the latter contributes to the level of functional vitamin A in the blood. In addition, they have suggested that as the rate of entry of vitamin A into the blood stream increases the amount reaching the Kupffer cells increases. If these postu-

92. Callison, E. C.; Orent-Keiles, E.; Frenchman, R., and Zook, E. G.: Comparison of Chemical Analysis and Bioassay as Measures of Vitamin A Value of Some Vegetables and the Effect of Comminution upon the Bioassay Value, J. Nutrition **37**:139, 1949.

93. Fell, H. B., and Mellanby, E.: Effects of Hypervitaminosis A on Foetal Mouse Bones Cultivated in Vitro, Brit. M. J. **2**:535, 1950.

94. Wilson, J. G., and Barch, S.: Fetal Death and Maldevelopment Resulting from Maternal Vitamin A Deficiency in the Rat, Proc. Soc. Exper. Biol. & Med. **72**:687, 1949.

95. Wilson, J. G., and Warkany, J.: Cardiac and Aortic Arch Anomalies in the Offspring of Vitamin A Deficient Rats Correlated with Similar Human Anomalies, Pediatrics **5**:708, 1950.

96. Glover, J., and Morton, R. A.: The Administration, Storage and Metabolism of Vitamin A, Biochem. J. **43**:xii, 1948.

lates are true, there may be an optimal rate of ingestion of vitamin A and a series of small doses may be preferable to a single large dose.

Vitamin A is now available in both oily and aqueous preparations. Lewis and associates [97] have demonstrated higher blood levels of vitamin A in infants following the administration of aqueous than of oily preparations. They also showed that absorption of vitamin A is related inversely to the particle size of the vehicle. A difference was noted in the absorption of vitamin A alcohol, acetate and natural esters when given in margarine,[98] but no difference was observed in absorption of the alcohol and ester (palmitate) in aqueous solution.[99] In rats liver storage was greater after administration of aqueous than of oily preparations. Aqueous preparations appear to be especially valuable in obstructive jaundice, cystic fibrosis of the pancreas and other diseases associated with poor absorption of fat.

An abnormality in the metabolism of vitamin A was reported in the nephrotic syndrome.[100] The high serum levels observed after administration of vitamin A were thought to be due to failure of utilization or storage by the liver.

In a clinical study of 106 persons, Chieffi and Kirk [101] found a higher incidence of hyperkeratosis of the skin follicles and of localized conjunctival thickening in subjects with low levels of vitamin A in the plasma (1 to 15 micrograms per 100 ml.) than in those with high levels (25 to 60 micrograms). Slightly more dryness of the skin and blepharoconjunctivitis were also observed in the former group. No correlation was found between dark adaptation time and plasma vitamin A values, but a significant correlation was observed between length of adaptation time and age. The percentage of keratinized cells in conjunctival smears was not clinically useful in evaluating vitamin A nutrition.

Anderson and co-authors [102] reported that massive parenteral doses of vitamin A were of value in the treatment of deafness and tinnitus.

Reports of hypervitaminosis A are becoming more numerous.[103] The syndrome is characterized by anorexia, loss of weight, irritability, low grade fever, pruriginous

97. Lewis, J. M., and Cohlan, S. Q.: Comparative Absorption of Various Types of Vitamin A Preparations, M. Clin. North America **34**:413, 1950. Lewis, J. M.; Cohlan, S. Q., and Messina, A.: Further Observations on the Absorption of Vitamin A.: Influence of the Particle Size of the Vehicle on the Absorption of Vitamin A, Pediatrics **5**:425, 1950.

98. Week, E. F., and Sevigne, F. J.: Vitamin A Utilization Studies: III. The Utilization of Vitamin A Alcohol, Vitamin A Acetate and Vitamin A Natural Esters by Humans, J. Nutrition **40**:563, 1950.

99. Kagan, B. M.; Jordan, D. A., and Gerald, P. S.: Absorption of Aqueous Dispersions of Vitamin A Alcohol and Vitamin A Ester in Normal Children, J. Nutrition **40**:275, 1950.

100. Kagan, B. M.; Thomas, E. M.; Jordan, D. A., and Abt, A. F.: Serum Vitamin A and Total Plasma Lipid Concentrations as Influenced by the Oral Administration of Vitamin A to Children with the Nephrotic Syndrome, J. Clin. Invest. **29**:141, 1950.

101. Chieffi, M., and Kirk, E.: Vitamin Studies in Middle-Aged and Old Individuals: II. Correlation Between Vitamin A Plasma Content and Certain Clinical and Laboratory Findings, J. Nutrition **37**:67, 1949.

102. Anderson, J. R.; Zoller, H. J., and Alexander, L. W.: Observations on the Treatment of Deafness and Tinnitus with Parenteral Vitamin A in Massive Doses (Lobel), Eye, Ear, Nose & Throat Month. **29**:75, 1950.

103. (*a*) Fried, C. T., and Grand, M. J. H.: Hypervitaminosis A, Am. J. Dis. Child. **79**: 475 (March) 1950. (*b*) Caffey, J.: Chronic Poisoning Due to Excess of Vitamin A: Description of the Clinical and Roentgen Manifestations in 7 Infants and Young Children, Pediatrics **5**:672, 1950. (*c*) Wyatt, T. C.; Carabello, C. A., and Fletcher, M. E.: Hypervitaminosis A: Report of a Case, J. A. M. A. **144**:304 (Sept. 23) 1950.

rash, sparseness of hair, hepatomegaly, tenderness over the long bones, evidence of periosteal elevation on roentgenologic examination and increase in the level of serum vitamin A. Fried [103a] postulated that the syndrome may be caused by hepatic dysfunction. The minimal toxic daily dose was about 75,000 international units, and the minimal latent period before the appearance of clinical signs was about six months.[103b] These findings emphasized that caution should be used in administration of vitamin A concentrates.

Vitamin B Complex.—Thiamine: Daum and associates [104] studied the physiological responses of healthy young women maintained on various levels of thiamine intake. Maximum work output and mechanical efficiency were the most sensitive physiological indexes of a decrease in dietary thiamine. The daily minimum requirement was considered to be 0.25 to 0.30 mg. per 1,000 calories for the majority of subjects. The thiamine requirement of the infant was determined by means of a urinary excretion procedure by Holt and collaborators [105] and was found to vary from 0.14 to 0.20 mg. per day in seven subjects. Schondel [106] studied thiamine excretion in children who had various types of illness and whose ages varied from 1 month to 14 years. Kirk and Chieffi [107] determined the concentrations of thiamine and pyruvic acid in the blood in middle-aged and old persons. The average concentration for thiamine was 3.4 γ and for pyruvic acid 1.1 mg. per 100 ml. There was a slight tendency for the thiamine value to decrease with age. Horwitt and Kreisler [108] have proposed a test for the diagnosis of mild thiamine deficiency. This consists of measuring the concentration of glucose, lactic acid and pyruvic acid in the blood after mild exercise and the ingestion of glucose, which constitute a "metabolic load" for the organism. The validity of the test was demonstrated by observations on subjects given controlled diets deficient in thiamine.

Garber and colleagues [109] have shown that a higher percentage of a dose of thiamine hydrochloride is excreted in the urine when the supplement is given with meals rather than between meals. When thiamine was administered with fresh bakers' yeast, none was returned in the urine, presumably because of failure of absorption.

Cases of contact dermatitis due to thiamine hydrochloride solutions have been reported.[110]

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104. Daum, K.; Tuttle, W. W., and Wilson, M.: Influence of Various Levels of Thiamine Intake on Physiologic Response: VII. Thiamine Requirements and Their Implications, J. Am. Dietet. A. **25**:398, 1949.

105. Holt, L. E., Jr.; Nemir, R. L.; Snyderman, S. E.; Albanese, A. A.; Ketron, K. C., and Corretero, R.: The Thiamine Requirement of the Normal Infant, J. Nutrition **37**:53, 1949.

106. Schondel, A.: Studies on the Urinary Excretion of Thiamine in Children, Acta pædiat. (Supp. 1) **35**:270, 1948.

107. Kirk, E., and Chieffi, M.: Vitamin Studies in Middle-Aged and Old Individuals: III. Thiamine and Pyruvic Acid Blood Concentration, J. Nutrition **38**:353, 1949.

108. Horwitt, M. K., and Kreisler, O.: The Determination of Early Thiamine-Deficient States by Estimation of Blood Lactic and Pyruvic Acids After Glucose Administration and Exercise, J. Nutrition **37**:411, 1949.

109. Garber, M.; Marquette, M. M., and Parsons, H. T.: The Availability of Vitamins from Yeast: V. Differences in the Influence of Live Yeast on the Absorption of Pure Thiamine Hydrochloride, Pure Riboflavin and Nitrogen by Human Subjects and the Effect of Distribution of the Vitamin Doses, J. Nutrition **38**:225, 1949.

110. Combes, F. C., and Groopman, J.: Contact Dermatitis Due to Thiamine: Report of 2 Cases, Arch. Dermat. & Syph. **61**:858 (May) 1950.

Beriberi continues to be an extremely important problem in many parts of the world. In the Philippines, where beriberi is endemic, an attempt is being made to reduce the incidence of thiamine deficiency by enrichment of polished rice with this substance. A preliminary clinical survey in Bataan, conducted by Salcedo and associates [111] in 1947, showed a high prevalence of beriberi. A number of biochemical studies were carried out in connection with this study by Burch and associates.[112] Patients with frank or suspected beriberi had significantly lower levels of blood thiamine than did persons without evidence of this deficiency state. Serum protein, hemoglobin and hematocrit values showed a progressive decrease with increasing severity of signs of beriberi. During the first year of enrichment of rice, there was a decline of 67.3 per cent in deaths from beriberi in the experimental area in which all rice was enriched, as compared with an increase of 2.4 per cent in a control zone in which only polished rice was available. Clinical resurvey in 1949 showed that in the experimental area nearly 90 per cent of persons who had shown symptoms two years previously had improved, and most of them were symptom free.

The improvement of nutrition of a population group by enrichment of a major foodstuff has also been demonstrated by recent studies in Newfoundland.[113] A striking decrease in signs and symptoms related to vitamin B complex deficiency occurred in that country between 1944 and 1948. This improvement appeared to be related, in large part, to the use of enriched flour beginning in 1944.

Riboflavin: Horwitt and co-authors [114] studied the effects of a diet containing 0.55 mg. of riboflavin in 2,200 calories in 15 male subjects over a period of nine to 17 months. During this time, angular stomatitis, seborrheic dermatitis, scrotal skin lesions and diminution of ability to perceive flicker were observed. Studies of the urinary excretion of riboflavin suggested that the riboflavin requirement of a resting adult is between 1.1 and 1.6 mg. per day. Since previous studies showed few abnormalities when the intake of riboflavin was above 0.6 mg. daily, it was concluded that allowances below this are insufficient to support normal repair of tissue. It was also suggested that the type of lesion encountered is dependent on the kind of injury to which the tissue is subjected. In a further report, Horwitt and associates [115] give data on riboflavin excretion in the urine at eight levels of dietary intake. They observed, also, that a subject depleted in riboflavin can assimilate satisfactorily at least 6 mg. of riboflavin at one time. A supplement of 6 mg. daily for 15 days was required for saturation in subjects depleted in riboflavin.

111. Salcedo, J., Jr.; Carrasco, E. O.; Jose, R. F., and Valenzuela, R. C.: Studies on Beriberi in an Endemic Sub-Tropical Area, J. Nutrition **36**:561, 1948.

112. Burch, H. B.; Salcedo, J., Jr.; Carrasco, E. O.; Intengan, C. L., and Caldwell, A. B.: Nutrition Survey and Tests in Bataan, Philippines, J. Nutrition **42**:9, 1950.

113. Goldsmith, G. A.; Darby, W. J.; Steinkamp, R. C.; Beam, A. S., and McDevitt, E.: Resurvey of Nutritional Status in Norris Point, Newfoundland, J. Nutrition **40**:41, 1950. Aykroyd, W. R.; Jolliffe, N.; Lowry, O. H.; Moore, P. E.; Sebrell, W. H.; Shank, R. E.; Tisdall, F. F.; Wilder, R. M., and Zamecnik, P. C.: Medical Resurvey of Nutrition in Newfoundland, 1948, Canad. M. A. J. **60**:329, 1949.

114. Horwitt, M. K.; Hills, O. W.; Harvey, C. C.; Liebert, E., and Steinberg, D. L.: Effect of Dietary Depletion of Riboflavin, J. Nutrition **39**:357, 1949.

115. Horwitt, M. K.; Harvey, C. C.; Hills, O. W., and Liebert, E.: Correlation of Urinary Excretion of Riboflavin with Dietary Intake and Symptoms of Ariboflavinosis, J. Nutrition **41**:247, 1950.

A fluorometric method for measuring free and total riboflavin in small quantities of blood serum and cells has been described by Burch and co-workers.[116]

Nicotinic Acid (Niacin): One of the nutrient interrelationships that has been widely studied is that of the amino acid, tryptophan, and the vitamin, nicotinic acid. It has been shown by Sarett and Goldsmith [117] and by Perlzweig and co-workers [118] that in man, as previously demonstrated in several animal species, tryptophan can be converted into nicotinic acid by the body. The site of this conversion and the chemical steps by which it is accomplished are still not completely known. Possible intermediate metabolites include kynurenine, 3-hydroxy-anthranilic acid and quinolinic acid.[119] It has been suggested that, rather than being converted to nicotinic acid in the tissues, tryptophan catalyzes the synthesis of nicotinic acid by intestinal bacteria.[120] This does not seem to be the case. Tryptophan administration was followed by an increase in urinary secretion of nicotinic acid compounds in the rat after enterectomy.[121] In man, the conversion of tryptophan to nicotinic acid was not affected by oral administration of streptomycin in amounts which largely inhibited the growth of coliform organisms in the intestinal tract.[122] Incontrovertible evidence that tryptophan is converted to nicotinic acid was demonstrated by Heidelberger and associates,[123] who administered tryptophan containing C^{14} in the 3-carbon of the indole ring to rats and recovered nicotinic acid with the isotope in the carboxyl group from the urine.

The administration of tryptophan to human beings is followed by an increase in the excretion of N^1-methylnicotinamide, the 6-pyridone of N^1-methylnicotinamide, quinolinic acid and tryptophan.[117c] Abnormalities in the excretion of tryptophan and nicotinic acid metabolites have been found in pellagra.[117c] Holman [124] reported that the excretion of the 6-pyridone of N^1-methylnicotinamide falls

116. Burch, H. A.; Bessey, O. A., and Lowry, O. H.: Fluorometric Measurements of Riboflavin and Its Natural Derivatives in Small Quantities of Blood Serum and Cells, J. Biol. Chem. **175**:457, 1948.

117. (*a*) Sarett, H. P., and Goldsmith, G. A.: The Effect of Tryptophan on the Excretion of Nicotinic Acid Derivatives in Humans, J. Biol. Chem. **167**:293, 1948; (*b*) Tryptophan and Nicotinic Acid Studies in Man, ibid. **177**:461, 1949; (*c*) Metabolism of L- and DL-Tryptophan in Normal Man and in Pellagrins, ibid. **182**:679, 1950.

118. Perlzweig, W. A.; Rosen, F.; Levitas, N., and Robinson, J.: The Excretion of Nicotinic Acid Derivatives After Ingestion of Tryptophan by Man, J. Biol. Chem. **167**:511, 1947.

119. Mitchell, H. K.; Nyc, J. F., and Owen, R. D.: Utilization by the Rat of 3-Hydroxyanthranilic Acid as a Substitute for Nicotinamide, J. Biol. Chem. **175**:433, 1948. Krehl, W. A.; Bonner, D., and Yanofsky, C.: Utilization of Niacin Precursors and Derivatives by the Rat and Neurospora, J. Nutrition **41**:159, 1950; Mechanism of Niacin Formation, Nutrition Rev. **8**:211, 1950.

120. Ellinger, P., and Kader, M. M. A.: The Nicotinamide-Saving Action of Tryptophane and the Biosynthesis of Nicotinamide by the Intestinal Flora of the Rat, Biochem. J. **44**:285, 1949; Role of Tryptophan in the Biosynthesis of Nicotinamide, Nature, London **163**:799, 1949.

121. Henderson, L. M., and Hankes, L. V.: Effect of Enterectomy on Synthesis of Niacin in the Rat, Proc. Soc. Exper. Biol. & Med. **70**:26, 1949.

122. Sarett, H. P., and Goldsmith, G. A.: Effect of Oral Administration of Streptomycin on B Vitamin Excretion in Man, Federation Proc. **9**:369, 1950.

123. Heidelberger, C.; Abraham, E. P., and Lepkovsky, S.: Tryptophan Metabolism: II. Concerning the Mechanism of the Mammalian Conversion of Tryptophan into Nicotinic Acid, J. Biol. Chem. **179**:151, 1949.

124. Holman, W. I. M., and de Lange, D. J.: Significance of Tryptophane in Human Nicotinic Acid Metabolism, Nature, London **165**:112, 1950.

to zero in this disease. The administration of tryptophan to patients with pellagra has been followed by healing of the lesions and return of the excretion pattern to normal.[125]

Comparative studies of nicotinic acid metabolism have shown that in man, dog, rat and pig excesses of the vitamin are largely disposed of by a methylating process, while in Herbivora and the polygastric species other pathways are probably involved.[126] In view of the complicated interrelationships of nicotinic acid in metabolism, the difficulties of estimating the human requirement for the substance, which is still largely unknown, are readily understood.

An interesting analysis of relationships of season, nutrient intake and the incidence of pellagra was presented by Sargent and Sargent.[127] The suggestion was made that a seasonal variation in the metabolism of man is a factor which changes the nutrient requirement of tissues and that this variation in requirement, rather than changes in nutrient intake, may explain the seasonal incidence of pellagra. If this is true, consideration should be given to this factor in investigating the human requirement of nutrients.

The incidence of pellagra has decreased notably in recent years in all parts of the United States. Bean and his colleagues [128] suggested that the most likely explanation of the decrease in Cincinnati, the area studied, was an improvement in the economic state of the population. Enrichment of flour and educational activities were thought to have sustained, but not to have initiated, the trend.

Frazier and associates [129] studied the nicotinic acid intake and excretion during pregnancy and noticed a significant increase in the excretion of N^1-methylnicotinamide during the last trimester. The response to the administration of a 50 mg. test dose of nicotinamide was also reported. Harris and Derian [130] suggested that the symptoms of bromide intoxication closely resemble those of pellagra and may possibly be due to nicotinic acid deficiency. When 750 mg. of nicotinamide was administered daily, symptoms of bromism disappeared, although the serum bromide level remained high.

Washburne [131] reported clinical improvement in 14 of 15 patients with depressive psychosis who were given nicotinic acid for its vasodilating action.

Pyridoxine: Although pyridoxine deficiency has been produced in experimental animals, attempts to find evidence of pyridoxine deficiency in man have been unsuc-

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125. Sarett and Goldsmith.[117e] Vilter, R. W.; Mueller, J. F., and Bean, W. B.: The Therapeutic Effect of Tryptophane in Human Pellagra, J. Lab. & Clin. Med. **34**:409, 1949.

126. Perlzweig, W. A.; Rosen, F., and Pearson, P. B.: Comparative Studies in Niacin Metabolism: The Fate of Niacin in Man, Rat, Dog, Pig, Rabbit, Guinea Pig, Goat, Sheep and Calf, J. Nutrition **40**:453, 1950.

127. Sargent, F., and Sargent, V. W.: Season, Nutrition and Pellagra, New England J. Med. **242**:447 and 507, 1950.

128. Bean, W. B.; Vilter, R. W., and Blankenhorn, M. A.: Incidence of Pellagra: Studies in the Cincinnati General Hospital 1935-1947, J. A. M. A. **140**:872 (July 9) 1949.

129. Frazier, E. I.; Porter T., and Humphrey, M. J.: The Utilization of Nicotinic Acid by Pregnant Women, J. Nutrition **37**:393, 1949.

130. Harris, R. S., and Derian, P. S.: Niacinamide in Bromide Intoxication, South. M. J. **42**:973, 1950.

131. Washburne, A. C.: Nicotinic Acid in the Treatment of Certain Depressed States: A Preliminary Report, Ann. Int. Med. **32**:261, 1950.

cessful until recently. Mueller and Vilter [132] administered desoxypyridoxine, a metabolic antagonist of pyridoxine, to eight subjects receiving a diet low in B complex vitamins. Seborrheic skin lesions developed about the eyes, nose and mouth after two to three weeks, and erosions about the mouth, resembling the cheilosis of riboflavin deficiency, appeared in about a month. Approximately half the patients showed glossitis and stomatitis morphologically similar to lesions of nicotinic acid deficiency. One subject had severe systemic symptoms: nausea, vomiting, weakness and dizziness. The lesions were not reversed by administration of a mixture containing thiamine, riboflavin and nicotinic acid but cleared within 48 to 72 hours after administration of pyridoxine. The authors suggest that the clinical picture represents at least part of the syndrome of acute human pyridoxine deficiency. The similarity of the lesions to those found in riboflavin and nicotinic acid deficiency indicates a close metabolic relationship among pyridoxine, nicotinic acid and riboflavin. Snyderman and associates [133] have reported the production of pyridoxine deficiency in two mentally defective infants who were given a diet deficient in pyridoxine. Pyridoxic acid disappeared from the urine; the total urinary pyridoxine was reduced to low values, and there was loss of the ability to convert tryptophan to nicotinic acid. Plateauing of the weight curve was observed for both infants. In addition, one infant had a series of convulsions which were promptly relieved by treatment with pyridoxine. The other infant showed a hypochromic anemia which responded rapidly to pyridoxine administration. After supplementation, a normal gain in weight was resumed. There was a delay in return of the ability to convert tryptophan to nicotinic acid.

Pyridoxine has been advocated in the treatment of nausea and vomiting of pregnancy, but the usefulness of this therapy remains uncertain. Dorsey [134] has reported that a combination of adrenal cortex extract and pyridoxine gives excellent results. No controls were used in the study, nor were results compared with those of other types of therapy. Critical evaluation must await further investigation.

Folic Acid (Pteroylglutamic Acid): Several reviews of the chemistry, physiology and clinical value of folic acid and other pteroylglutamates have been published recently.[135] The distribution of folic acid in foods is incompletely known and is complicated by lack of information concerning the relative activities for man of the three naturally occurring pteroylglutamates, folic acid (monoglutamate), fermentation factor (triglutamate) and the heptaglutamate. Good sources of the vitamin appear to be fresh green leafy vegetables and organ meats, while fair sources are lean beef and veal and wheat cereals.[135c]

There has been much interest in the use of folic acid antagonists, i. e., pterins structurally related to folic acid. Some of these antagonists have been shown to inhibit the growth of spontaneous and transplanted tumors in animals. In leukemia

132. Mueller, J. F., and Vilter, R. W.: Pyridoxine Deficiency in Human Beings Induced with Desoxypyridoxine, J. Clin. Invest. **29**:193, 1950.

133. Snyderman, S.; Carretero, R., and Holt, L. E., Jr.: Pyridoxine Deficiency in the Human Being, Federation Proc. **9**:371, 1950.

134. Dorsey, C. W.: The Use of Pyridoxine and Suprarenal Cortex Combined in the Treatment of the Nausea and Vomiting of Pregnancy, Am. J. Obst. & Gynec. **58**:1073, 1949.

135. (*a*) Jukes, T. H., and Stokstad, E. L. R.: Pteroylglutamic Acid and Related Compounds, Physiol. Rev. **28**:51, 1948. (*b*) Wilkinson, J. F.: Folic Acid, Brit. M. J. **1**:771 and 822, 1948. (*c*) Present Knowledge of Pteroylglutamates ("Folic Acid"), Nutrition Rev. **8**: 260, 1950.

in man, temporary remissions have been induced in about one third of the cases by therapy with several antagonists but cure has not been demonstrated.[136] Toxic manifestations following administration of antagonists represent the syndrome of folic acid deficiency, namely, glossitis, diarrhea, gastrointestinal lesions and anemia.

The metabolic role of folic acid is still uncertain, but it seems probable that folic acid functions as an enzyme in combination with a specific protein. Allfrey and King[137] have presented evidence of a folic acid-protein complex in yeast, but an enzyme effect has not been demonstrated. Folic acid appears to be related to tyrosine metabolism and perhaps also to ascorbic acid. Abnormal excretion of metabolites of tyrosine occurs in scorbutic guinea pigs and in human infants with scurvy when the diet is high in this amino acid. Folic acid will prevent or relieve this abnormal excretion (as does ascorbic acid) in guinea pigs[138] and in infants if very large doses are administered.[139] Additional evidence of relationship between folic acid and ascorbic acid is the inconstant hemopoietic effect of ascorbic acid in adult scurvy and the association of megaloblastic anemia of infancy with diets low in vitamin C.[138] Dietrich and co-workers[140] have indicated that ascorbic acid and vitamin B_{12} stimulate synthesis of folic acid in the body, as shown by increased stores in the liver. May[141] found that ascorbic acid administration will prevent the development of anemia in monkeys deficient in folic acid. However, only folic acid will stimulate a hemopoietic response if the anemia has been permitted to occur.

There is much evidence that folic acid has a role in the reproductive process. Diets low in folic acid impair reproduction in the rat.[142] Folic acid is necessary for the characteristic tissue response to estrogen administration in both the monkey and the chick.[143] The requirement of folic acid in the rat is increased during lactation.[144]

There is some relationship between folic acid and thymine; in man, thymine possesses hemopoietic activity similar to that of folic acid, but much larger doses are

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136. Dameshek, W.: The Use of Folic Acid Antagonists in the Treatment of Acute and Subacute Leukemia, Blood **4**:168, 1949. Farber, S.: Some Observations on the Effect of Folic Acid Antagonists on Acute Leukemia and Other Forms of Incurable Cancer, ibid. **4**:160, 1949. Burchenal, J. H.; Karnofsky, D. A.; Southam, C. M.; Myers, W. P. L.; Carver, L. F.; Dargeon, H. W., Jr., and Rhoads, C. P.: Clinical Experiences with the 4-Amino Derivatives of Pteroylglutamic Acid and 2, 6-Diaminopurine in the Treatment of Neoplastic Disease, Am. J. Med. **7**:420, 1949.

137. Allfrey, V. G., and King, C. G.: An Investigation of the Folic Acid-Protein Complex in Yeast, J. Biol. Chem. **182**:367, 1950.

138. Woodruff, C. W.; Cherrington, M. E.; Stockell, A. K., and Darby, W. J.: The Effect of Pteroylglutamic Acid and Related Compounds upon Tyrosine Metabolism in the Scorbutic Guinea Pig, J. Biol. Chem. **178**:861, 1949.

139. Morris, J. E.; Harpur, E. R., and Goldbloom, A.: The Metabolism of l-Tyrosine in Infantile Scurvy, J. Clin. Invest. **29**:325, 1950.

140. Dietrich, L. S.; Nichol, C. A.; Monson, W. J., and Elvehjem, C. A.: Observations on the Interrelation of Vitamin B_{12}, Folic Acid, and Vitamin C in the Chick, J. Biol. Chem. **181**: 915, 1949.

141. May, C. D., and others, cited in Nutrition Rev. **8**:264, 1950.

142. Nelson, M. M., and Evans, H. M.: Pteroylglutamic Acid and Reproduction in the Rat, J. Nutrition **38**:11, 1949.

143. Hertz, R.: Interference with Estrogen-Induced Tissue Growth in the Chick Genital Tract by a Folic Acid Antagonist, Science **107**:300, 1948.

144. Williamson, M. B.: Increased Requirement for Pteroylglutamic Acid During Lactation, Proc. Soc. Exper. Biol. & Med. **70**:336, 1949.

required.[145] Vilter and co-workers [146] have suggested that folic acid exerts its hematological effect in pernicious anemia by "mass action" and that it may be essential for the formation or utilization of thymine and other pyrimidines and purines. Neurological lesions appeared in persons receiving increasing doses of folic acid to maintain hematological remission. This suggests that in pernicious anemia folic acid may push a chemical reaction through to completion in persons already deficient in vitamin B_{12} and further deplete the body supply of this factor, with the result that combined system disease develops.

A relationship between folic acid and choline metabolism has been mentioned previously in this review in the discussion of methyl metabolism and liver disease.

A substance that appears to be a metabolite of folic acid was discovered in the course of studies in which the micro-organism Leuconostoc citrovorum was employed.[147] Citrovorum factor, as the substance is termed, is excreted in human and rat urine, and the excretion is increased following administration of folic acid.[148] The activity of citrovorum factor is greater than that of folic acid for some organisms.[149] Nichol and Welch [150] have shown that folic acid may be converted to citrovorum factor in vitro by liver slices and that this conversion is aided by ascorbic acid. If this conversion of folic acid is found to be essential to its biologic function, a possible explanation of relationships between folic acid and ascorbic acid will be provided.

The therapeutic usefulness of folic acid has been reviewed by Dameshek.[151] This vitamin is effective in the treatment of sprue, nutritional macrocytic anemia, macrocytic anemia of pregnancy and megaloblastic anemia of infancy. Vitamin B_{12} therapy is rarely useful in the last two anemias mentioned.[135c] Although use of folic acid will not prevent the development of neurological lesions in patients with pernicious anemia, it has been demonstrated that folic acid does not exert a toxic effect on the nervous system.[152] An instance of hypersensitivity to folic acid has been reported.[153]

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145. Spies, T. D.; Frommeyer, W. B.; Vilter, C. F., and English, A.: Anti-Anemic Properties of Thymine, Blood **1**:185, 1946.

146. Vilter, R. W.; Horrigan, D.; Mueller, J. F.; Jarrold, T.; Vilter, C. F.; Hawkins, V., and Seaman, A.: Studies on Relationships of Vitamin B_{12}, Folic Acid, Thymine, Uracil and Methyl Group Donors in Persons with Pernicious Anemia and Related Megaloblastic Anemias, Blood **5**:695, 1950.

147. Sauberlich, H. E., and Baumann, C. A.: A Factor Required for the Growth of Leuconostoc Citrovorum, J. Biol. Chem. **176**:165, 1948.

148. Sauberlich, H. E.: The Effect of Folic Acid upon the Urinary Excretion of the Growth Factor Required by Leuconostoc Citrovorum, J. Biol. Chem. **181**:467, 1949.

149. A New Form of Folic Acid: The Leuconostoc Citrovorum Factor, Nutrition Rev. **8**:282, 1950.

150. Nichol, C. A., and Welch, A. D.: Synthesis of Citrovorum Factor from Folic Acid by Liver Slices: Augmentation by Ascorbic Acid, Proc. Soc. Exper. Biol. & Med. **74**:52, 1950.

151. Dameshek, W.: Folic Acid, Pernicious Anemia and Pendulums, Blood **3**:699, 1948.

152. Weissberg, J.; McGavack, T. H.; Vogel, M., and Kenigsberg, S.: The Effect of Folic Acid on the Central Nervous System of Normal Subjects and Subjects with Anemia Other Than Pernicious Anemia, Blood **5**:148, 1950. Harvey, E. A.; Howard, I., and Murphy, W. P.: Absence of a Toxic Effect of Folic Acid on the Central Nervous System of Persons Without Pernicious Anemia, New England J. Med. **242**:446, 1950. Poliakoff, H.; Sternbach, A.; Walker, W. A.; Kascht, R. L., and Meyer, L. M.: Administration of Folic Acid to Patients Without Anemia, Proc. Soc. Exper. Biol. & Med. **72**:392, 1949.

153. Mitchell, D. C.; Vilter, R. W., and Vilter, C. F.: Hypersensitivity to Folic Acid, Ann. Int. Med. **31**:1102, 1949.

In rats folic acid will prevent leukopenia and granulocytopenia induced by thiouracil and propylthiouracil feeding.[154] Cameron and colleagues[155] have induced macrocytic anemia in rats by surgically producing intestinal defects. Treatment with folic acid increased survival time and stimulated hematological remission. Further study of these experimental anemias may assist in understanding the pathogenesis of certain macrocytic anemias in man.

SPRUE

Observations on the clinical features and pathogenesis of the sprue syndrome have been presented by several investigators.[156] The etiological basis and pathogenesis of sprue remain obscure. Woodruff[156b] found a seasonal incidence of tropical sprue which paralleled the appearance of amebic dysentery and suggested an infective origin. Davidson and Fountain[156d] and Bartley[157] noted a familial incidence of idiopathic steatorrhea and celiac disease and postulated a genetic element in pathogenesis. Tropical sprue is frequently a reversible disease, particularly if treatment is initiated early.[156a,b] In nontropical sprue full rehabilitation and remission may not be achieved.[158] Studies on the absorption of hexoses and of several forms of vitamin A in patients with sprue were reported by Fox.[159]

VITAMIN B_{12}

Vitamin B_{12} has been the subject of extensive research since it was isolated in 1948 by Rickes and associates[160] and by Smith[161] and was demonstrated to have anti-pernicious-anemia activity by West.[162] Originally isolated from liver, vitamin B_{12} was later obtained by fermentation from Streptomyces (Actinomyces) griseus.[163]

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154. Delor, R. A., and Petering, R. G.: The Action of Pteroylglutamic Acid on Blood Dyscrasias Induced by Thiouracil and Propylthiouracil, Blood **5**:155, 1950.

155. Cameron, D. G.; Callender, S. T. E.; Watson, G. M., and Witts, L. J.: Experimental Macrocytic Anemia in the Rat Treated with Purified Liver Extract, Pteroylglutamic Acid and Vitamin B_{12}, Nature, London **164**:188, 1949.

156. (*a*) Stefanini, M.: Clinical Features and Pathogenesis of Tropical Sprue, Medicine **27**:379, 1948. (*b*) Woodruff, A. W.: Aetiological and Prognostic Features in Tropical Sprue, Tr. Roy. Soc. Trop. Med. & Hyg. **42**:605, 1949. (*c*) Preuss, J.: Etiology and Pathogenesis of Sprue, Am. Pract. **3**:400, 1949. (*d*) Davidson, L. S. P., and Fountain, J. R.: Incidence of the Sprue Syndrome with Some Observations on the Natural History, Brit. M. J. **1**:1157, 1950.

157. Bartley, C. W.: Steatorrhoea in a Family, Brit. M. J. **1**:1161, 1950.

158. Fox, H. J.: Clinical and Laboratory Residuals in Patients Treated for Sprue, Am. J. Med. **7**:241, 1949.

159. Fox, H. J.: Absorption of Unemulsified and Emulsified Vitamin A in Sprue, J. Lab. & Clin. Med. **34**:1140, 1949; Sucrose Absorption in Sprue, ibid. **35**:622, 1950.

160. Rickes, E. L.; Brink, N. G.; Koniuszy, F. R.; Wood, T. R., and Folkers, K.: Crystalline Vitamin B_{12}, Science **107**:396, 1948.

161. Smith, E. L., and Parker, L. F. J.: Purification of Anti-Pernicious Anaemia Factor, Biochem. J. **43**:viii, 1948. Smith, E. L.: Purification of Anti-Pernicious Anaemia Factor from Liver, Nature, London **161**:636, 1948.

162. West, R.: Activity of Vitamin B_{12} in Addisonian Pernicious Anemia, Science **107**:398, 1948.

163. Rickes, E. L.; Brink, N. G.; Koniuszy, F. R.; Wood, T. R., and Folkers, K.: Comparative Data on Vitamin B_{12} from Liver and from a New Source, Streptomyces Griseus, Science **108**:634, 1948.

Vitamin B_{12} is a red crystalline compound containing cobalt,[164] the structure of which has been only partly elucidated. Several closely related compounds with vitamin B_{12} activity have been discovered.[165] Vitamin B_{12b} has been found to have an effect in man comparable to that of Vitamin B_{12}.[166] Thymidine will replace vitamin B_{12} as a growth factor for bacteria[167] but has not stimulated blood regeneration in Addisonian pernicious anemia in the amounts tested.[168] The animal protein factor, which is necessary for growth in a number of animal species, appears to be identical with or very similar to vitamin B_{12}.[169]

Assay methods for determining the vitamin B_{12} content of foods, bodily fluids and commercial antianemic preparations are not completely satisfactory. Microbiologic assay with Lactobacillus leichmannii[170] appears preferable to that with Lactobacillus lactis dorner, the micro-organism used initially by Shorb.[171] Vitamin B_{12} (crystalline and concentrate) has been admitted by interim revision to the United States Pharmacopeia XIII, but, in view of lack of agreement on a standardized method of assay for this vitamin, liver preparations will continue to be labeled with U. S. P. unitage.[172]

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164. Rickes, E. L.; Brink, N. G.; Koniuszy, F. R.; Wood, T. R., and Folkers, K.: Vitamin B_{12}, A Cobalt Complex, Science **108**:134, 1948. Smith, E. L.: Presence of Cobalt in the Anti-Pernicious Anaemia Factor, Nature, London **162**:144, 1948.

165. Lichtman, H.; Watson, J.; Ginsberg, V.; Pierce, J. V.; Stokstad, E. L. R., and Jukes, T. H.: Vitamin B_{12}: Some Properties and Its Therapeutic Use, Proc. Soc. Exper. Biol. & Med. **72**:643, 1949. Cuthbertson, W. F. J., and Smith, E. L.: Chromatography of the Vitamin B_{12} Group of Factors, Biochem. J. **44**:v, 1949.

166. Watson, J.; Lichtman, H.; Ginsberg, V.; Pierce, J. V.; Stokstad, E. L. R., and Jukes, T. H.: Use of Vitamin B_{12b} in Pernicious Anemia, Am. J. Med. **8**:398, 1950. Spies, T. D.; Stone, R. E.; Koch, M. B.; Grant, H. M., and Moore, M. M.: The Hemopoietic Response of Patients with Pernicious Anemia to Crystalline Vitamin B_{12b}, South. M. J. **43**:50, 1950.

167. Thymidine and Vitamin B_{12} in Pernicious Anemia, Nutrition Rev. **8**:20, 1950.

168. Reisner, E. H., and West, R.: Effect of Thymine Desoxyriboside (Thymidine) on Human Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **71**:651, 1949. Ungley, C. C.: Thymidine and Vitamin B_{12} in Pernicious Anemia, Lancet **1**:164, 1949.

169. (*a*) Nichol, C. A.; Dietrich, L. S.; Cravens, W. W., and Elvehjem, C. A.: Activity of Vitamin B_{12} in the Growth of Chicks, Proc. Soc. Exper. Biol. & Med. **70**:40, 1949. (*b*) Ott, W. H.; Rickes, E. L., and Wood, T. R.: Activity of Crystalline Vitamin B_{12} for Chick Growth, J. Biol. Chem. **174**:1047, 1948. (*c*) Neumann, A. L.; Johnson, B. C., and Thiersch, J. B.: Crystalline Vitamin B_{12} in the Nutrition of the Baby Pig, J. Nutrition **40**:403, 1950. (*d*) Stokstad, E. L. R.; Page, A.; Pierce, J.; Franklin, A. L.; Jukes, T. H.; Heinle, R. W.; Epstein, M., and Welch, A. D.: Activity of Microbial Animal Protein Factor Concentrates in Pernicious Anemia, J. Lab. & Clin. Med. **33**:860, 1948.

170. Stokstad, E. L. R.; Dornbush, A. C.; Franklin, A. L.; Hoffman, C. E.; Hutchings, B. L., and Jukes, T. H.: Microbiological Assay of Vitamin B_{12} by Lactobacillus Leichmannii, Federation Proc. **8**:257, 1949. Skeggs, H. R.; Huff, J. W.; Wright, L. D., and Bosshardt, D. K.: The Use of Lactobacillus Leichmannii in the Microbiological Assay of the "Animal Protein Factor," J. Biol. Chem. **176**:1459, 1948. Peeler, H. T.; Yacowitz, H., and Norris, L. C.: A Microbiological Assay for Vitamin B_{12} Using Lactobacillus Leichmannii, Proc. Soc. Exper. Biol. & Med. **72**:515, 1949. Thompson, H. T.; Dietrich, L. S., and Elvehjem, C. A.: The Use of Lactobacillus Leichmannii in the Estimation of Vitamin B_{12} Activity, J. Biol. Chem. **184**:175, 1950.

171. Shorb, M. S.: Activity of Vitamin B_{12} for the Growth of Lactobacillus Lactis, Science **107**:397, 1948.

172. Heinle, R. W.: Communication of U. S. P. Anti-Anemia Preparations Advisory Board.

Some knowledge of the distribution of vitamin B_{12} in foods has been obtained. Glandular meats are excellent sources; muscle tissue, eggs and milk contain lesser amounts. Plant materials show no measurable activity.[173]

Many papers dealing with the effects of vitamin B_{12} in pernicious anemia and other macrocytic anemias have appeared, and there is abundant evidence that vitamin B_{12} is the erythrocyte maturation factor of liver. When vitamin B_{12} is administered parenterally to patients with pernicious anemia in relapse, there are a prompt rise in reticulocytes and a return of the erythrocyte and hemoglobin levels to normal. Satisfactory hematological response has been induced by the daily administration of 1 microgram of vitamin B_{12}, and it has been suggested that 1 microgram of the vitamin is approximately equivalent to 1 unit of liver extract.[174] Ungley [175] studied the response of 73 patients to a single dose of vitamin B_{12} and found that the rate of regeneration was roughly proportional to the logarithm of the dose. Jones and Darby [176] and Goldsmith [177] suggested that an average daily dose of approximately 3 micrograms may be necessary to obtain a maximum rate of erythropoiesis. When vitamin B_{12} is given in amounts averaging more than 2 micrograms daily, the hemotological response is comparable to that which follows administration of liver extract.[177]

The requirement of vitamin B_{12} for maintenance therapy has been reported to vary from less than 0.3 to 4 micrograms daily, when injections were given at intervals of one to four weeks.[178] While many patients have been satisfactorily controlled with 1 microgram per day, others have shown a decrease in erythrocytes and hemoglobin content with this dosage.[179] Larger amounts of vitamin B_{12} might pro-

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173. Lewis, U. J.; Register, U. D.; Thompson, H. T., and Elvehjem, C. A.: Distribution of Vitamin B_{12} in Natural Materials, Proc. Soc. Exper. Biol. & Med. **72**:479, 1949. Register, U. D.; Lewis, U. J.; Thompson, H. T., and Elvehjem, C. A.: Variations in the Vitamin B_{12} Content of Selected Samples of Pork and Beef Muscle, ibid. **70**:167, 1949.

174. (*a*) West, R., and Reisner, E. H., Jr.: Treatment of Pernicious Anemia with Crystalline Vitamin B_{12}, Am. J. Med. **6**:643, 1949. (*b*) Mueller, J. F.; Jarrold, T.; Hawkins, V. R., and Vilter, R. W.: The Effect of Vitamin B_{12} on the Hematologic and Neurologic Manifestations of Pernicious Anemia, Ohio M. J. **46**:225, 1950. (*c*) Hall, B. E., and Campbell, D. C.: Vitamin B_{12} Therapy in Pernicious Anemia: II. Effect on the General Clinical and Neurologic Manifestations; Preliminary Report, Proc. Staff Meet., Mayo Clin. **23**:591, 1948. (*d*) Beard, M. F.; Nataro, M., and Layman, L. H.: Vitamin B_{12} in Pernicious Anemia, South. M. J. **42**:677, 1949. (*e*) Bethell, F. H.; Meyers, M. C., and Neligh, R. B.: Vitamin B_{12} in Pernicious Anemia and Puerperal Macrocytic Anemia, J. Lab. & Clin. Med. **33**:1477, 1948.

175. Ungley, C. C.: Vitamin B_{12} in Pernicious Anemia: Parenteral Administration, Brit. M. J. **2**:1370, 1949.

176. Jones, E., and Darby, W. J.: Pernicious Anemia and Related Anemias Treated with Vitamin B_{12}, Blood **4**:827, 1949.

177. Goldsmith, G. A.: Effects of Vitamin B_{12} Given Orally and Parenterally and of a Concentrate of Intrinsic Factor in Macrocytic Anemia, Proceedings of the International Society of Hematology, Third International Congress, Cambridge, England, Aug. 22, 1950, New York, Grune & Stratton, Inc., 1951.

178. (*a*) Mueller and others.[174b] (*b*) Ungley.[175] (*c*) Goldsmith.[177] (*d*) Bethell, F. H.: Treatment of Macrocytic Anemias with Vitamin B_{12}, J. Am. Dietet. A. **26**:89, 1950. (*e*) Recent Work on Vitamin B_{12}, Medical Societies, Lancet **1**:353, 1950.

179. (*a*) Beard, M. F.; McIlvanine, S. K., and Nataro, M.: Vitamin B_{12} in Pernicious Anemia in Remission, South. M. J. **43**:678, 1950. (*b*) Meacham, G. C.; Vignos, P. J.; Heinle, R. W.; Weisberger, A. S., and Epstein, M.: Vitamin B_{12} Concentrate in the Maintenance of Pernicious Anemia, J. Lab. & Clin. Med. **35**:713, 1950.

duce satisfactory results in these subjects, but the possibility remains that vitamin B_{12} may not be a complete replacement for liver extract.[180]

Vitamin B_{12} is effective in relieving all the clinical signs in pernicious anemia, including glossitis[181] and neurological lesions.[182] Peripheral neuritis and subacute combined degeneration of the spinal cord improve rapidly in patients treated with vitamin B_{12}, and there are no reports of appearance of these lesions in persons maintained with this vitamin. Vitamin B_{12} has been used successfully in persons sensitive to liver extract.[183]

There has been much interest in the relationship between vitamin B_{12} and Castle's extrinsic and intrinsic factors. In pernicious anemia the oral administration of vitamin B_{12} rarely stimulates hemopoiesis unless large doses are used.[184] If normal human gastric juice is given simultaneously or within two hours after oral administration of vitamin B_{12}, hemopoietic response is induced.[185] The potentiation of vitamin B_{12} by intrinsic factor in gastric juice suggests that extrinsic factor is identical with or similar to vitamin B_{12}, which is presumably identical with the anti-

180. Beard and others.[179a] Owren, P. A., in discussion at Meeting of International Society of Hematology, Cambridge, England, Aug. 22, 1950. Jacobson, B., and Bishop, R. C.: Studies of the Principle in Liver Effective in Pernicious Anemia: VII. The Augmentative Effect of Accessory Factors on Therapeutic Activity of Vitamin B_{12}, J. Clin. Invest. **28**:791, 1949.

181. Stone, R. E., and Spies, T. D.: The Effect of Liver Extract and Vitamin B_{12} on the Mucous Membrane Lesions of Macrocytic Anemia, J. Lab. & Clin. Med. **33**: 1019, 1948. Schieve, J. F., and Rundles, R. W.: Response of Lingual Manifestations of Pernicious Anemia to Pteroylglutamic Acid and Vitamin B_{12}, ibid. **34**:439, 1949.

182. Hall and Campbell.[174c] Berk, L.; Denny-Brown, D.; Finland, M., and Castle, W. B.: Effectiveness of Vitamin B_{12} in Combined System Disease: Rapid Regression of Neurologic Manifestations and Absence of Allergic Reactions in a Patient Sensitive to Injectable Liver Extracts, New England J. Med. **239**:328, 1948. Hall, B. E.; Krusen, F. H., and Woltman, H. W.: Vitamin B_{12} and Coordination Exercises for Combined Degeneration of the Spinal Cord in Pernicious Anemia, J. A. M. A. **141**:257 (Sept. 24) 1949. Ungley, C. C.: Subacute Combined Degeneration of the Cord: I. Response to Liver Extracts; II. Trials with Vitamin B_{12}; Appendix: Quantitative Method of Assessing Neurologic Status, Brain **72**:382, 1949. Mettier, S. R.; McBride, A., and Tat, R.: The Effect of Vitamin B_{12} on the Anemia and Combined System Disease of Addisonian Pernicious Anemia, California Med. **71**:21, 1949.

183. Berger, H.: Vitamin B_{12} in Addisonian Pernicious Anemia in a Liver Sensitive Person, New York J. Med. **50**:331, 1950. Murray, M. Y., and Propp, S.: Vitamin B_{12} Effective in Pernicious Anemia with Combined System Disease and Liver Sensitivity, ibid. **49**:2570, 1949.

184. (*a*) Goldsmith.[177] (*b*) Hall, B. E.; Morgan, E. H., and Campbell, D. C.: Oral Administration of Vitamin B_{12} in Pernicious Anemia: I. Presence of Intrinsic Factor in Berkefeld-Filtered Pooled Human Gastric Juice; Preliminary Report, Proc. Staff Meet., Mayo Clin. **24**:99, 1949. (*c*) Bethell, F. H.; Swendseid, M. E.; Meyers, M. C.; Neligh, R. B., and Richards, H. G.: Observations on the Hemopoietic Factors in Hog Stomach and Duodenum, and the Treatment of Pernicious Anemia by Orally Administered Vitamin B_{12} in Combination with Extracts of Duodenal Mucosa, Univ. Hosp. Bull., Ann Arbor **15**:49, 1949. (*d*) Spies, T. D.; Stone, R. E.; Lopez, G. G.; Milanes, F.; Toca, R. L., and Aramburu, T.: Vitamin B_{12} by Mouth in Pernicious and Nutritional Macrocytic Anaemia and Sprue, Lancet **2**:454, 1949.

185. Hall and others.[184b] (*b*) Berk, L.; Castle, W. B.; Welch, A. D.; Heinle, R. W.; Anker, R., and Epstein, M.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: X. Activity of Vitamin B_{12} as Food (Extrinsic) Factor, New England J. Med. **239**:911, 1948. (*c*) Campbell, D. C.; Hall, B. E., and Morgan, E. H.: Oral Administration of Vitamin B_{12} in Pernicious Anemia: II. Studies on the Nature and Source of Intrinsic Factor, J. Lab. & Clin. Med. **34**:1590, 1949.

pernicious-anemia principle of liver. Further substantiation of this hypothesis has been obtained by Morgan and Gardner and their associates,[186] who observed that parenterally administered extracts of beef muscle stimulate hemopoiesis. The activity of beef muscle could be explained on the basis of its vitamin B_{12} content.[186a] Other studies have demonstrated the presence of intrinsic factor in extracts of hog stomach and duodenum. Oral administration of vitamin B_{12} in combination with these extracts to patients with pernicious anemia has been followed by hemopoietic response which was often maximal.[187]

The structure of intrinsic factor and its exact role in hemopoiesis remain to be determined. Vitamin B_{12} does not appear to be changed by incubation with normal gastric juice.[188] Large amounts of vitamin B_{12} have been found in the feces of pernicious anemia patients,[189] and fecal extracts have been shown to have antianemic activity when given parenterally.[190] Vitamin B_{12} appears to be synthesized in the human colon,[191] and it has been suggested that human requirements may be met from this source. From these observations and the findings noted above, it seems probable that the function of intrinsic factor is to facilitate absorption of vitamin B_{12} or related compounds from the intestinal tract rather than to combine with extrinsic factor as previously postulated. The manner in which intrinsic factor promotes absorption is unknown. Ternberg and Eakin[192] have shown that normal gastric juice contains a heat-labile, nondialyzable substance, presumably a protein, which unites with vitamin B_{12} to form a complx that cannot be used for growth of micro-organisms, such as L. lactis. The substance in gastric juice may be intrinsic factor, and perhaps the complex which is formed, by some mechanism, protects vitamin B_{12} from destruction or enhances its absorption.[193]

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186. (*a*) Morgan, E. H.; Hall, B. E., and Campbell, D. C.: Hematopoietic Activity of Parenterally Administered Beef Muscle Concentrate in Cases of Pernicious Anemia, Proc. Staff Meet., Mayo Clin. **24**:594, 1949. (*b*) Gardner, F. H.; Harris, J. W.; Schilling, R. F., and Castle, W. B.: Observations on Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: XI. Hematopoietic Activity in Pernicious Anemia of a Beef Muscle Extract Containing Food (Extrinsic) Factor upon Intravenous Injection Without Contact with Gastric (Intrinsic) Factor, J. Lab. & Clin. Med. **34**:1502, 1949.

187. Goldsmith.[177] Bethell and others.[184c] Hall, B. E.; Bethell, F. H.; Morgan, E. H.; Campbell, D. C.; Swendseid, M. E.; Miller, S., and Cintron-Rivera, A. A.: Observations on the Presence of Intrinsic Factor in Extracts of Hog Stomach and Duodenum, Proc. Staff Meet., Mayo Clin. **25**:105, 1950. Hall, B. E.: Intrinsic Factor of Castle, Brit. M. J. **2**:585, 1950. Spies, T. D.; Lopez, G. G.; Milanes, F.; Toca, R. L., and Reboredo, A.: Antianemic Properties of a Reaction Product of Vitamin B_{12} and the Intrinsic Factor, South. M. J. **43**:206, 1950.

188. Wolf, D. E.; Wood, T. R.; Valiant, J., and Folkers, K.: Vitamin B_{12} and the Intrinsic Factor, Proc. Soc. Exper. Biol. & Med. **73**:15, 1950.

189. Bethell and others.[174e] Berk and others.[185b]

190. Callender, S. T. E.; Mallett, B. J.; Spray, G. H., and Shaw, G. E.: Anti-Anaemia Activity of Faecal Extract from Pernicious Anaemia Patient, Lancet **2**:57, 1949.

191. Girdwood, R. H.: Vitamin B_{12} and Pernicious Anaemia, Lancet **1**:594, 1950. Dyke, W. J. C.; Hind, H. G.; Riding, D., and Shaw, G. E.: Bacterial Synthesis of Vitamin B_{12} in the Alimentary Tract, Brit. M. J. **1**:486, 1950.

192. Ternberg, J. L., and Eakin, R. E.: Erythein and Apoerythein and Their Relation to the Anti-Pernicious Anemia Principle, J. Am. Chem. Soc. **71**:3858, 1949.

193. Vitamin B_{12} and the Intrinsic Factor, Nutrition Rev. **8**:165, 1950.

Vitamin B_{12} has been shown to be an effective therapeutic agent in sprue and nutritional macrocytic anemia when administered parenterally.[194] In a few patients with idiopathic steatorrhea and megaloblastic anemia, vitamin B_{12} therapy has been reported to be ineffectual.[195] Vitamin B_{12}, administered orally in doses of 5 to 10 micrograms daily, stimulated clinical and hematological improvement in about 50 per cent of subjects with sprue or nutritional macrocytic anemia who received this therapy.[177] Persons who failed to respond to use of vitamin B_{12} were greatly benefited by folic acid therapy. In the treatment of megaloblastic anemia of infancy, vitamin B_{12} has been found to be effective in some cases, ineffective in others. In the latter administration of folic acid was followed by definite improvement.[196] It seems likely that sprue, nutritional macrocytic anemia and megaloblastic anemia of infancy are syndromes of varied origin.

Macrocytic anemia of pregnancy has been uninfluenced by use of vitamin B_{12} in most instances, whereas a favorable response is usually obtained with folic acid therapy.[197] In India, Patel [198] reported improvement in patients with this type of anemia following treatment with vitamin B_{12}.

Meyer and associates [199] have suggested that folic acid potentiates orally administered vitamin B_{12}. Adequate control periods were not included in these studies, and findings may be due to additive rather than potentiating effects.

A number of articles reviewing current investigation of vitamin B_{12} and its role in macrocytic anemia have appeared.[200]

194. Goldsmith.[177] Spies, T. D.; Stone, R. E., and Aramburu, T.: Observations on the Anti-Anemia Properties of Vitamin B_{12}, South. M. J. **41**:522, 1948. Suarez, R. M.; Spies, T. D.; Morales, F. H., and Perez, E.: A Note on the Effectiveness of Vitamin B_{12} in the Treatment of Tropical Sprue in Relapse, Blood **4**:1124, 1949. Patel, J. C.: Crystalline Anti-Pernicious Anemia Factor in Treatment of 2 Cases of Tropical Macrocytic Anemia, Brit. M. J. **2**:934, 1948.

195. Tuck, I. M., and Whittaker, N.: Vitamin B_{12} in Idiopathic Steatorrhea, Lancet **1**:757, 1950.

196. McPherson, A. Z.; Jonsson, U., and Rundles, R. W.: Vitamin B_{12} Therapy in Megaloblastic Anemia of Infancy, J. Pediat. **34**:529, 1949. Sturgeon, P., and Carpenter, G.: Megaloblastic Anemia of Infancy: Response to Vitamin B_{12}, Blood **5**:458, 1950. Woodruff, C. W.; Ripy, H. W.; Peterson, J. C., and Darby, W. J.: Variable Response to Vitamin B_{12} of Megaloblastic Anemia of Infancy, Pediatrics **4**:723, 1949.

197. Day, L. A.; Hall, B. E., and Pease, G. L.: Macrocytic Anemia of Pregnancy Refractory to Vitamin B_{12} Therapy: Response to Therapy with Folic Acid; Report of a Case, Proc. Staff Meet., Mayo Clin. **24**:149, 1949. Furman, R. H.; Daniels, W. B.; Hefner, L. L.; Jones, E., and Darby, W. J.: Pernicious Anemia of Pregnancy; Failure of Vitamin B_{12} Therapy; Successful Treatment with Folic Acid; Report of a Case, Am. Pract. **1**:146, 1950. Ungley, C. C., and Thompson, R. B.: Vitamin B_{12} and Folic Acid in Megaloblastic Anemias of Pregnancy and the Puerperium, Brit. M. J. **1**:919, 1950.

198. Patel, J. C., and Kocher, B. R.: Vitamin B_{12} in Macrocytic Anemia of Pregnancy and the Puerperium, Brit. M. J. **1**:924, 1950.

199. Meyer, L. M.; Sawitsky, A.; Ritz, N. D., and Krim, M.: Oral Treatment of Pernicious Anemia with Subminimal Doses of Folic Acid and Vitamin B_{12}, Am. J. Clin. Path. **20**:454, 1950.

200. Bethell.[178d] Progress with Vitamin B_{12}, editorial, Lancet **2**:565, 1949. Vitamin B_{12} and Pernicious Anaemia, editorial, ibid. **1**:500, 1950. Campbell, D. C.; Hall, B. E., and Morgan, E. H.: The Treatment of Pernicious Anemia and Other Macrocytic Anemias with Vitamin B_{12}, M. Clin. North America **34**:1197, 1950. Dameshek, W.: And Now B_{12}! Blood **4**:76, 1949. Davis, L. J.: Vitamin B_{12}, Practitioner **165**:77, 1950. Jones, E.: Vitamin B_{12}, Am. Pract. **3**:391, 1949. Reisner, E. H., Jr.: The Present Status of Vitamin B_{12} in Pernicious Anemia, Bull. New York Acad. Med. **25**:429, 1949. Spies, T. D.; Suarez, R. M.; Lopez, G. G.; Milanes, F.; Stone, R. E.; Toca, R. L.; Aramburu, T., and Kartus, S.: Tentative Appraisal of Vitamin B_{12} as a Therapeutic Agent, J. A. M. A. **139**:521 (Feb. 19) 1949.

For some time, vitamin B_{12} has been recognized as a growth factor in animals. Recently, Wetzel and co-workers [201] administered 10 micrograms of vitamin B_{12} daily by mouth to 11 children with malnutrition and simple growth failure. Changes in growth were measured by the Wetzel Grid technique. Five of the 11 subjects responded with definite and significant improvement. It may be presumed that these children were deficient in vitamin B_{12} or were in need of an increased supply of this vitamin. Downing [202] was unable to promote growth in premature infants by administration of vitamin B_{12}. Further studies of the effects of vitamin B_{12} on human growth will be awaited with interest.

Bean and colleagues [203] reported dramatic relief of pain in three patients with nutritional neuropathy following injections of vitamin B_{12}. Eleven patients with painful neurological disorders of non-nutritional orgin were not benefited. Vitamin B_{12} treatment failed to initiate improvement in patients with amyotrophic lateral sclerosis.[204]

On the basis of animal experiments, vitamin B_{12} may be expected to be useful in the treatment of a number of clinical conditions other than those discussed above. Interrelationships of vitamin B_{12}, methionine, choline and folic acid have already been mentioned.[59] This vitamin may prove useful in the treatment of hepatic injury,[205] protein deficiency and thyrotoxicosis.[206]

CHOLINE

Best [207] has reviewed the subject of choline and its precursors as lipotropic agents. Reference has been made to interrelationships of choline, methionine, folic acid and vitamin B_{12} earlier in this review. The reported benefit of choline in the therapy of coronary arteriosclerosis has also been mentioned. Hartroft and Best [208] have described the development of hypertension of renal origin in rats which were maintained on a choline-deficient diet for less than one week early in life. Handler

201. Wetzel, N. C.; Fargo, W. C.; Smith, I. H., and Helikson, J.: Growth Failure in School Children as Associated with Vitamin B_{12} Deficiency: Response to Oral Therapy, Science **110**:651, 1949.

202. Downing, D. F.: Failure of Vitamin B_{12} to Promote Growth of Premature Infants, Science **112**:181, 1950.

203. Bean, W. B.; Franklin, M., and Sahs, A. L.: An Effect of Vitamin B_{12} on Pain in Nutritional Neuropathy, Am. J. M. Sc. **220**:431, 1950.

204. Spies, T. D., and Stone, R. E.: Some Observations on Patients with Amyotrophic Lateral Sclerosis, South. M. J. **42**:410, 1949.

205. Popper, H.; Koch-Weser, D., and Szanto, P. B.: Protective Effect of Vitamin B_{12} upon Hepatic Injury Produced by Carbon Tetrachloride, Proc. Soc. Exper. Biol. & Med. **71**:688, 1949. Gyorgy, P., and Rose, C. S.: Effect of Vitamin B_{12} on Experimental Hepatic Injury, ibid. **73**:372, 1950. B_{12} and Fatty Liver, editorial, South. M. J. **43**:171, 1950. Drill, V. A., and McCormick, H. M.: Lipotropic Effects of Vitamin B_{12} Concentrate, Proc. Soc. Exper. Biol. & Med. **72**:388, 1949.

206. Nichol and others.[169a] Emerson, G. A.: Growth Promoting Activity of Vitamin B_{12} in Rats Receiving Thyroid Substance, Proc. Soc. Exper. Biol. & Med. **70**:392, 1949. Betheil, J. J., and Lardy, H. A.: Comparative Effectiveness of Vitamin B_{12}, Whole Liver Substance and Extracts High in APA Activity, as Growth Promoting Materials for Hyperthyroid Animals, J. Nutrition **37**:495, 1949.

207. Best, C. H.: Protection of Liver and Kidneys by Dietary Factors: Choline and Its Precursors as Lipotropic Agents, Federation Proc. **9**:506, 1950.

208. Hartroft, W. S., and Best, C. H.: Hypertension of Renal Origin in Rats Following Less Than One Week of Choline Deficiency in Early Life, Brit. M. J. **1**:423, 1949.

and Bernheim [209] have corroborated these findings. The ability of choline and related compounds to protect the rat from the renal hemorrhagic syndrome of choline deficiency has been studied by Welch.[210]

INOSITOL

Little is known about the role of inositol in nutrition. It has been found to be a lipotropic agent in animals under certain conditions.[211] Felch and Dotti [212] have observed that inositol is an effective agent in lowering serum cholesterol and lipid phosphorus levels in patients who have diabetes mellitus with hypercholesteremia.

ASCORBIC ACID

Present concepts of vitamin C nutrition in man have been reviewed by King.[213] Burns and colleagues [214] synthesized radioactive *l*-ascorbic acid and studied its metabolism in normal and scorbutic guinea pigs. Radioactivity amounting to 20 to 30 per cent of the injected dose appeared in respiratory carbon dioxide during 24 hours; urine contained 3 to 6 per cent of total activity and feces 0.7 per cent. Calcium oxalate, isolated from urine, contained 60 per cent of the total urine activity, demonstrating a precursor role of ascorbic acid in oxalate formation. Radiocarbon was also incorporated into purified benzin (petroleum ether) fractions extracted from the spleen and adrenal glands of scorbutic guinea pigs. Ascorbic acid is known to be related to the functional activity of the adrenal cortex, but the biochemical mechanisms are obscure. Dumm and Ralli [215] presented evidence that in the rat ascorbic acid may be synthesized in the adrenal gland. Dugal and Therien [216] found that administration of large doses of ascorbic acid to rats during exposure to cold increased survival, permitted better growth and prevented the adrenal enlargement noted in untreated animals. Wallach and Reineke,[217] in studies of rats treated with thyroxin, presented evidence in favor of the hypothesis that changes in adrenal weight and ascorbic acid content which occur during stress reflect changes in the output of adrenocortical hormones.

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209. Handler, P., and Bernheim, F.: Influence of Dietary Factors on Hypertension Induced by Choline Deficiency, Am. J. Physiol. **162**:189, 1950.

210. Welch, A. D.: The Relation of the Structure of Choline-like Compounds to Renal Antihemorrhagic Action, J. Nutrition **40**:113, 1950.

211. Brown, R. A., and Sturtevant, M.: Inositol, in Harris, R. S., and Thimann, K. V.: Vitamins and Hormones: Advances in Research and Applications, New York, Academic Press, Inc., 1949, vol. 7, p. 185.

212. Felch, W. C., and Dotti, L. B.: Depressing Effect of Inositol on Serum Cholesterol and Lipid Phosphorus in Diabetes, Proc. Soc. Exper. Biol. & Med. **72**:376, 1949.

213. King, C. G.: Vitamin C, J. A. M. A. **142**:563 (Feb. 25) 1950.

214. Burns, J. J.; Burch, H. B., and King, C. G.: Studies on Radioactive L-Ascorbic Acid, Federation Proc. **9**:157, 1950.

215. Dumm, M. E., and Ralli, E. P.: The Excretion of Pantothenic Acid and Ascorbic Acid by Intact and Adrenalectomized Rats on Diets Supplemented with and Deficient in Pantothenic Acid, Endocrinology **45**:188, 1949.

216. Dugal, L. P., and Therien, M.: The Influence of Ascorbic Acid on the Adrenal Weight During Exposure to Cold, Endocrinology **44**:420, 1949.

217. Wallach, D. P., and Reineke, E. P.: The Effect of Varying Levels of Thyroidal Stimulation on the Ascorbic Acid Content of the Adrenal Cortex, Endocrinology **45**:75, 1949.

Lewin and Wassén [218] reported a beneficial effect of simultaneous administration of ascorbic acid and desoxycorticosterone in rheumatoid arthritis. Both confirmation and negation of these findings have appeared.[219] Hallberg [220] assumed that the effectiveness of desoxycorticosterone acetate and ascorbic acid may have been due to oxidation of the steroid by ascorbic acid, and he tried substitution of methylene blue for the vitamin. Slight but definite objective improvement was noted after administration of either ascorbic acid or methylene blue. A possible interpretation of the findings is that desoxycorticosterone acetate is oxidized by ascorbic acid to yield a product with a physiological effect similar to that of cortisone. In experimental arthritis in rats, combined injections of desoxycorticosterone and ascorbic acid exerted a beneficial effect.[221] McKee and associates [222] obtained data indicating that scorbutic guinea pigs break down glycogen at a slower rate than normal and have difficulty in synthesizing glycogen. Administration of adrenal cortex extract or 11-dehydrocorticosterone, as a gluconeogenic stimulant, failed to increase liver glycogen in scorbutic animals. Further experimentation is essential before it can be assumed that ascorbic acid is specifically needed for the synthesis and breakdown of glycogen.

Several studies of the relationship between ascorbic acid intake and the level of ascorbic acid in the serum or plasma in man have been reported.[223] A statistical analysis of data from three nutrition surveys showed a significant correlation between dietary intake and plasma level of ascorbic acid.[223c] Dodds [223b] calculated that "utilization" of ascorbic acid at several levels of intake was approximately 1 mg. per kilogram of body weight. Todhunter and co-authors [224] presented data indicating that dehydroascorbic acid was satisfactorily utilized by the body.

A number of studies on the relationship between ascorbic acid and tyrosine metabolism have appeared.[225] In scurvy the use of high protein diets or the admin-

218. Lewin, E., and Wassén, E.: Effect of Combined Injections of Deoxycortone Acetate and Ascorbic Acid on Rheumatoid Arthritis, Lancet **2**:993, 1949.

219. Ascorbic Acid and Desoxycorticosterone in Rheumatic Disease, Nutrition Rev. **8**:276, 1950.

220. Hallberg, L.: Effect of Deoxycortone and Methylene-Blue in Rheumatoid Arthritis: An Attempt to Explain the Action of Ascorbic Acid on Deoxycortone, Lancet **1**:351, 1950.

221. Brownlee, G.: Effect of Deoxycortone and Ascorbic Acid on Formaldehyde-Induced Arthritis in Normal and Adrenalectomized Rats, Lancet **1**:157, 1950.

222. McKee, R. A.; Cobbey, T. S., Jr., and Geiman, Q. M.: The Effect of Administered Adrenal Cortical Hormones on the Liver Glycogen of Normal and Scorbutic Guinea Pigs, Endocrinology **45**:21, 1949.

223. (*a*) Storvick, C. A.; Davey, B. L.; Nitchals, R. M.; Coffey, R. E., and Fincke, M. L.: Ascorbic Acid Metabolism of Older Adolescents, J. Nutrition **39**:1, 1949. (*b*) Dodds, M. L.; Price, E. L., and MacLeod, F. L.: A Study of the Relation and Adjustment of Blood Plasma Level and Urinary Excretion of Ascorbic Acid to Intake, ibid. **40**:255, 1950. (*c*) Putman, P.; Milam, D. F.; Anderson, R. K.; Darby, W. J., and Mead, P. A.: The Statistical Association Between the Diet Record of Ascorbic Acid Intake and the Blood Content of the Vitamin in Surveyed Populations: I. A Statistical Reconnaissance, Milbank Mem. Fund Quart. **27**:355, 1950.

224. Todhunter, E. N.; McMillan, T., and Ehmke, D. A.: Utilization of Dehydroascorbic Acid by Human Subjects, J. Nutrition **42**:297, 1950.

225. Woodruff and others.[138] Morris and others.[139] Woodruff, C. W.: Tyrosine Metabolism in Infantile Scurvy, J. Lab. & Clin. Med. **36**:640, 1950. Rogers, W. F., Jr., and Gardner, F.: Tyrosine Metabolism in Human Scurvy, J. Clin. Invest. **28**:806, 1949.

istration of tyrosine leads to hydroxyphenyluria. The excretion of abnormal quantities of hydroxyphenyl derivatives may be prevented by administration of ascorbic acid or, as previously noted, of large amounts of folic acid.

VITAMIN D

Jeans [226] has reviewed the requirements, sources and functions of vitamin D, as well as therapy with this vitamin and signs of toxicity which follow administration of excessive doses. Recent studies have added information concerning the antagonism between phytate and vitamin D. Phytate, which is present in large quantities in cereals, has long been known to decrease the absorption of calcium from the intestinal tract of animals on diets inadequate in vitamin D. Mellanby [227] has shown that phytate may exercise an anticalcifying action in puppies even when vitamin D is provided. Phytate also appears to interfere with the absorption of calcium from the human intestinal tract.[228] The antagonistic action of phytate on vitamin D, as observed in animals, may be applicable in human nutrition.

Gray and Carter [229] have emphasized the value of determining plasma alkaline phosphatase levels in the early diagnosis of rickets. The most frequent diagnostic titer lay between 25 and 40 units. Estimation of blood phosphatase three weeks after the administration of 200,000 units of calciferol was found to be a useful procedure in borderline cases. Clark and Beck [230] have studied 1,252 subjects and presented normative data for plasma alkaline phosphatase activity for persons from birth to the age of 27 years.

Freeman and Dunsky [231] described observations in a case of resistant rickets and discussed the syndrome on the basis of their findings and others reported in the literature. The nature of the underlying defect responsible for the development of resistant rickets is unknown, but there appears to be interference with the normal calcifying action of vitamin D. In the case reported evidences of healing were obtained without correction of all the metabolic defects.

Instances of vitamin D intoxication continue to be reported, particularly in association with the use of massive doses of this vitamin in the treatment of rheumatoid arthritis.[232] Reed [233] has reviewed the factors involved in pathological calcification brought about by an excess of vitamin D and has presented new data obtained from experiments in dogs.

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226. Jeans, P. C.: Vitamin D, J. A. M. A. **143**:177 (May 13) 1950.

227. Mellanby, E.: The Rickets-Producing and Anti-Calcifying Action of Phytate, J. Physiol. **109**:488, 1949.

228. Phytic Acid, Vitamin D, and Absorption of Calcium, Nutrition Rev. **8**:59, 1950.

229. Gray, J. D., and Carter, F. S.: The Early Diagnosis of Rickets, Arch. Dis. Childhood **24**:189, 1949.

230. Clark, L. C., and Beck, E.: Plasma "Alkaline" Phosphatase Activity: I. Normative Data for Growing Children, J. Pediat. **36**:335, 1950.

231. Freeman, S., and Dunsky, I.: Resistant Rickets, Am. J. Dis. Child. **79**:409 (March) 1950.

232. Addis, H. St. C. C., and Currie, R. D.: Hypercalcaemia During Vitamin D Treatment of Rheumatoid Arthritis, Brit. M. J. **1**:877, 1950. Hyde, J. S., and Richmond, J. B.: Vitamin D Intoxication in a Child with Rheumatoid Arthritis, Am. J. Dis. Child. **80**:379 (Sept.) 1950.

233. Reed, C. I.: Vitamin D and Tissue Calcification, Am. Pract. **1**:164, 1950.

Calciferol has been found to be useful in the treatment of lupus vulgaris and other types of cutaneous tuberculosis.[234] Large doses which are just below toxic levels must be employed in conjunction with the usual tuberculosis regimen. A high percentage of cures has been obtained.

VITAMIN E

No claim for a role of vitamin E in human nutrition has yet been substantiated. The Council on Pharmacy and Chemistry of the American Medical Association [235] stated in 1949 that vitamin E had not been shown to be of benefit in the treatment of heart disease, other cardiovascular conditions or diabetes mellitus. Eichert [236] evaluated current reports and reached similar conclusions. Bensley and co-authors [237] in a carefully controlled study failed to obtain any evidence supporting the view that vitamin E was of value in the treatment of diabetes mellitus. Mean values for plasma tocopherol were found to be normal in patients with diabetes.[238] Plasma levels could not be related to dietary intake of vitamin E but were related to levels of plasma cholesterol.

Owens and Owens [239] have reported that administration of large amounts of *dl*-alpha-tocopherol acetate will prevent retrolental fibroplasia, a disease which develops in some premature infants shortly after birth and which leads to impaired vision or blindness. The study was carefully conducted, and interpretation of findings was conservative. In view of the large doses of tocopherol used, the vitamin may be acting through a pharmacologic mechanism rather than as a corrective for deficiency. Nevertheless, the results are important from a therapeutic standpoint.

Kay and collaborators [240] have observed that administration of a water-soluble salt of alpha tocopherol and calcium will increase the antithrombin level in the blood and largely prevent intravascular clotting after surgical procedures. The findings are interesting and, if corroborated, will be a valuable contribution to preventive therapy of phlebothrombosis.

Harris [241] has analyzed a number of foods for tocopherol content. The richest dietary sources of vitamin E are certain vegetable oils, cereal products and eggs; vegetables supply little of the daily intake.

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234. Calciferol in Lupus Vulgaris, editorial, J. A. M. A. **141**:726 (Nov. 5) 1949. Escalona, E.; Estrada, M. C.; Arias, O., and Chevez, A.: Cutaneous Tuberculosis and Its Treatment with Calciferol, M. Woman's J. **57**:7, 1950.

235. Vitamin E, report of the Council on Pharmacy and Chemistry, J. A. M. A. **142**:485 (Feb. 18) 1950.

236. Eichert, H.: Vitamin E: A Therapeutic Perpetration, South. M. J. **42**:717, 1949.

237. Bensley, E. H.; Fowler, A. F.; Creaghan, M. V.; Zahalan, F.; Lax, F.; Berish, H., and McDonald, E. K.: Trial of Vitamin E Therapy in Diabetes Mellitus, Canad. M. A. J. **61**:260, 1949.

238. Bensley, E. H.; Fowler, A. F.; Creaghan, M. V.; Moore, B. A., and McDonald, E. K.: Plasma Tocopherol in Diabetes Mellitus, J. Nutrition **40**:323, 1950.

239. Owens, W. C., and Owens, E. U.: Retrolental Fibroplasia in Premature Infants: II. Studies on the Prophylaxis of the Disease; The Use of Alpha Tocopherol Acetate, Am. J. Ophth. **32**:1631, 1949.

240. Kay, J. H.; Balla, G.; Hutton, S., and Ochsner, A.: The Prophylaxis of Intravascular Clotting by the Use of Alpha Tocopherol and Calcium, New Orleans M. & S. J. **103**:116, 1950.

241. Harris, P. L.; Quaife, M. L., and Swanson, W. J.: Vitamin E Content of Foods, J. Nutrition **40**:367, 1950.

VITAMIN K

Although numerous studies have been carried out on problems of blood coagulation in the past year, little of the work is related to vitamin K or has a nutritional component. Several new techniques for determining prothrombin time have been suggested.[242] Mann and co-authors [243] compared the coagulation defect of vitamin K deficiency with that caused by bishydroxycoumarin (dicumarol®). Vitamin K deficiency produced a greater decrease in prothrombin than in cothromboplastin, while the reverse was true for bishydroxycoumarin. Miller and associates [244] found that water-soluble vitamin K preparations had no antagonistic effect on bishydroxycoumarin, while vitamin K_1 and vitamin K_1 oxide were effective in decreasing prothrombin time. Consequently, it is recommended that either vitamin K_1 or its oxide, or blood transfusion, be employed in the treatment of hemorrhage following use of bishydroxycoumarin.

Administration of sulfadiazine had no effect on prothrombin concentration in newborn infants when administered in amounts of 1 grain per pound (0.13 gm. per kilogram) of body weight for three days.[245] It, therefore, appears safe to prescribe these drugs in the newborn without the use of vitamin K as adjunct therapy.

MINERAL NUTRITION

Review of the many studies which have been conducted on problems of water and electrolyte balance cannot be included here. Newer methods for determining body water [246] and for measuring several electrolytes in plasma and urine [247] have been developed and evaluated. A simple bedside method for determination of chloride has been proposed.[248] Practical suggestions concerning fluid and electrolyte

242. Losner, S.; Volk, B. W.; Jacobi, M., and Newhouse, S.: Photoelectric Determination of Prothrombin Time, J. Lab. & Clin. Med. **36**:473, 1950. Schwager, P. G., and Jaquer, L. B.: A Simplified Technique for the Determination of Prothrombin Time, Canad. M. A. J. **60**:258, 1949. Stefanini, M.: New One Stage Procedure for the Quantitative Determination of Prothrombin and Labile Factor, Am. J. Clin. Path. **20**:233, 1950.

243. Mann, F. D.; Mann, J. D., and Bollman, J. L.: The Coagulation Defect of Vitamin K Deficiency Compared with That Caused by Dicumarol, J. Lab. & Clin. Med. **36**:234, 1950.

244. Miller, R.; Harvey, W. P., and Finch, C. A.: Antagonism of Dicumarol by Vitamin K Preparations, New England J. Med. **242**:211, 1950.

245. Kane, S., and Benton, C.: Prothrombin in the Newborn Infant: VI. Effect of Sulfadiazine on Prothrombin of the Newborn, J. Pediat. **37**:90, 1950.

246. Steele, J. M.: Body Water, Am. J. Med. **9**:141, 1950. Steele, J. M.; Berger, E. Y.; Dunning, M. F., and Brodie, B. B.: Total Body Water in Man, Am. J. Physiol. **162**:313, 1950. Levitt, M. F., and Gaudino, M.: Measurement of Body Water Compartments, Am. J. Med. **9**:208, 1950.

247. Mosher, R. E.; Boyle, A. J.; Bird, E. J.; Jacobson, S. D.; Batchelor, T. M.; Iseri, L. T., and Myers, G. B.: The Use of Flame Photometry for the Quantitative Determination of Sodium and Potassium in Plasma and Urine, Am. J. Clin. Path. **19**:461, 1949. Smith, R. G.; Craig, P.; Bird, E. J.; Boyle, A. J.; Iseri, L. T.; Jacobson, S. D., and Myers, G. B.: Spectrochemical Values for Sodium, Potassium, Iron, Magnesium, and Calcium in Normal Human Plasma, ibid. **20**:263, 1950.

248. Scribner, B. H.: Bedside Determination of Chloride: A Method for Plasma, Urine and Other Fluids and Its Application to Fluid Balance Problems, Proc. Staff Meet., Mayo Clin. **25**:209, 1950.

therapy, as outlined in several recent publications, should prove most useful to the clinician.[249]

The role of potassium in disease, the diagnosis of potassium deficiency and the importance of potassium in therapy, particularly in relation to diabetic acidosis, have been subjects to which much attention has been directed. Several recent reviews deal adequately with current knowledge of potassium in nutrition.[250] The human requirements of calcium, phosphorus and magnesium have been reviewed by Stearns.[251] Calcium retention in adolescent girls has been studied by Johnston and co-workers.[252] In an investigation of neonatal tetany, Dodd and Rapoport[253] reported a parallelism between the occurrence and severity of symptoms of tetany and the decrease in concentration of serum calcium. In infants with tetany the level of serum calcium was less than 9 mg. per 100 ml. in all instances. The concentration of serum phosphorus was above 8 mg. per 100 ml. in one third of the subjects. Gardner and associates[254] suggested that the factors responsible for the occurrence of tetany are limitation in renal excretion of phosphorus in the neonatal period, due perhaps to insufficient parathyroid function, and the feeding of cow's milk with its relatively high content of phosphorus.

Iron and copper in nutrition have been reviewed by Darby,[255] and a symposium on copper metabolism has been published.[256] Much of our recent knowledge of iron metabolism has come from studies with radioactive iron.[257] Present concepts concerning the absorption and utilization of iron and certain other aspects of iron metabolism have been discussed in several recent papers.[258] The importance of gastric hydrochloric acid in the release of iron from food and the influence of ascorbic acid and protein digestion products in reducing iron to the ferrous state have been reemphasized. Evidence that iron synthesis occurs in the immature erythrocyte has been presented. Studies of the dermal loss of iron indicate very little loss in sweat

249. Darrow, D. C., and Pratt, E. L.: Fluid Therapy: Relation to Tissue Composition and the Expenditure of Water and Electrolyte, J. A. M. A. **143**:365 (May 27); 432 (June 3) 1950. Lich, R., Jr., and Maurer, J. E.: Some Practical Considerations Concerning Fluid and Electrolyte Therapy, South. M. J. **43**:542, 1950. Wilson, B.: Clinical Approach to Problems in Water and Salt Metabolism, ibid. **42**:73, 1949. Bodansky, O.: Parenteral Fluid Therapy, M. Clin. North America **34**:395, 1950.

250. Kahn and Stare.[66b] Danowski, T. S.: Newer Concepts of the Role of Potassium in Disease, Am. J. Med. **7**:525, 1949. Darrow, D. C.: Body Fluid Physiology: The Role of Potassium in Clinical Disturbances of Body Water and Electrolyte, New England J. Med. **242**:1014, 1950. Nadler, C. S.; Bellet, S.; Gazes, P. C., and Steiger, W. A.: Administration of Potassium to Patients with Prolonged Vomiting and Diabetic Acidosis, J. Lab. & Clin. Med. **35**:842, 1950. Elkinton, J. R., and Tarail, R.: The Present Status of Potassium Therapy, Am. J. Med. **9**:200, 1950.

251. Stearns, G.: Human Requirements of Calcium, Phosphorus and Magnesium, J. A. M. A. **142**:478 (Feb. 18) 1950.

252. Johnston, F. A.; Schlaphoff, D., and McMillan, T.: Calcium Retained from One Level of Intake by Six Adolescent Girls, J. Nutrition **41**:137, 1950.

253. Dodd, K., and Rapoport, S.: Hypocalcemia in the Neonatal Period: Clinical Study, Am. J. Dis. Child. **78**:537 (Oct.) 1949.

254. Gardner, L. I.; MacLachlan, E. A.; Pick, W.; Terry, M. L., and Butler, A. M.: Etiologic Factors in Tetany of Newly Born Infants, Pediatrics **5**:228, 1950.

255. Darby, W. J.: Iron and Copper, J. A. M. A. **142**:1288 (April 22) 1950.

256. Glass, B.: Symposium on Copper Metabolism, Science **112**:209, 1950.

257. Moore, C. V.: Light on Iron Requirement, J. Am. Dietet. A. **26**:598, 1950.

258. Brunton, L.: An Outline of Iron Metabolism, Canad. M. A. J. **63**:74, 1950. Recent Studies of Iron, editorial, J. A. M. A. **142**:904 (March 25) 1950.

which is free of cells, but some loss is associated with desquamation.[259] In studies of iron metabolism during normal pregnancy, no evidence was obtained suggesting that iron deficiency occurred in any phase.[260]

In infections the level of serum iron falls rapidly, and anemia occurs if the infection is not eradicated. The iron-binding capacity of the serum is reduced, but this does not account for the hypoferremia, as shown by observations of Cartwright and Wintrobe.[261] Gubler and colleagues [262] have reported that inflammation in rats is associated with a decrease in iron absorption which may be counteracted by use of cobalt. If this is found to be true in man, it will offer a possible explanation for the reported efficacy of cobalt therapy in the anemias of infection. Kuhns and coworkers [263] failed to correct hypoferremia or to induce reticulocytosis in anemias of infection when large doses of saccharated oxide of iron were administered intravenously. In only a few subjects was there a suggestive increase in hemoglobin content. In a patient who died, most of the iron administered was recoverable from the liver.

There are few indications for intravenous iron therapy. If the patient is unable to tolerate iron given orally, saccharated iron oxide administered intravenously is effective in treating hypochromic anemia due to iron deficiency. The dose should be only that calculated to correct the deficiency because of the potential danger of tissue damage over long periods from excessive iron deposits.[264] Severe toxic reactions may occur when attempts are made to replace iron stores by a single intravenous dose. The toxic effects resemble symptoms of paroxysmal hemoglobinuria.[264c]

Tests of iron-molybdenum preparations have failed to demonstrate that molybdenum improves iron absorption.[265] Granick,[266] discussing iron metabolism in hemochromatosis, has suggested that dietary measures may be helpful in limiting iron absorption. Several cases of ferrous sulfate poisoning have been described by Thompson.[267]

259. Dermal Loss of Iron, editorial, J. A. M. A. **144**:47 (Sept. 2) 1950.

260. Rath, C. E.; Caton, W.; Reid, D. E.; Finch, C. A., and Conroy, L.: Hematological Changes and Iron Metabolism of Normal Pregnancy, Surg., Gynec. & Obst. **90**:320, 1950.

261. Cartwright, G. E., and Wintrobe, M. M.: Chemical, Clinical and Immunological Studies on the Products of Human Plasma Fractionation: XXXIX. The Anemia of Infection; Studies on the Iron Binding Capacity of Serum, J. Clin. Invest. **28**:86, 1949.

262. Gubler, C. J.; Cartwright, G. E., and Wintrobe, M. M.: Influence of Inflammation, Cobalt Administration, Diet and Pyridoxine Deficiency on Iron Absorption, Am. J. Med. **8**:537, 1950.

263. Kuhns, W. J.; Cartwright, G. E., and Wintrobe, M. M.: Anemia of Infection: Clinical Experiences with Ferrivenin, Am. J. Med. **8**:523, 1950.

264. (*a*) Brown, E. B.; Moore, C. V.; Reynafarje, C., and Smith, D. E.: Intravenously Administered Saccharated Iron Oxide in the Treatment of Hypochromic Anemia: Therapeutic Results, Potential Dangers and Indications, J. A. M. A. **144**:1084 (Nov. 25) 1950. (*b*) Harrigan, D. L.; Mueller, J. F., and Vilter, R. W.: Observations on the Intravenous Administration of Saccharated Oxide of Iron in Human Beings, J. Lab. & Clin. Med. **36**:422, 1950. (*c*) Ramsey, A. S.: Intravenous Iron in the Treatment of Anaemia, Brit. M. J. **1**:1109, 1950.

265. Gullberg, S., and Vahlquist, B.: The Efficiency of an Iron-Molybdenum Preparation as Evaluated by Means of Iron Absorption Tests, Blood **5**:871, 1950.

266. Granick, S.: Iron Metabolism and Hemochromatosis, Bull. New York Acad. Med. **25**:403, 1949.

267. Thompson, J.: Ferrous Sulfate Poisoning, Its Incidence, Symptomatology, Treatment and Prevention, Brit. M. J. **1**:645, 1950.

NUTRITION IN DENTAL CARIES

Current theories of the etiology of dental caries include poor nutrition and inadequate diets, high carbohydrate diets, inherently poor tooth structure and high counts of lactic acid-producing bacteria in the oral cavity.[268] One school of thought emphasizes the importance of oral environment; another, the constitutional aspect.[269] Studies at the University of Iowa [270] have stressed the importance of the state of nutrition as a factor in dental caries. Children maintained on nutritionally adequate diets have shown complete arrest of caries, regardless of the sugar content of the diet. King [271] administered supplements of sweets to infants at bedtime without producing an increase in dental caries. The infants' diets were high in carbohydrate, relatively high in vitamins A and D and fairly satisfactory in calcium and phosphorous content. Cioffari [272] observed a low incidence of caries in a group of children on a diet containing few sweets but including coarse foods and vitamin supplements. The incidence of caries was much greater in a second group receiving a diet high in sweets and irregular in vitamin supplements. Toverud [273] reported a decrease in dental caries in Norway during World War II with an increase following the war. Factors which may have influenced this trend include (1) preferential rationing of protective foods during the war to pregnant and lactating women and to children up to 6 years of age and (2) a decrease in consumption of carbohydrate, meat and fat during the war, with an increase in high extraction flour, potatoes, vegetables and fish.

The influence of fluorine in the prevention of dental caries is being studied in several communities in which fluoridation of water has been introduced. In the Newburgh-Kingston study fluorine has been added to the water supply in the former city, the latter acting as a control area.[274] After three years of water fluoridation, the number of decayed, missing and filled teeth in Newburgh has decreased from 21.0 to 14.8 per 100, while in Kingston it has remained at 21.3 per 100.

In previous studies of the oral environmental factor in caries production, it was reported that a higher concentration of ammonia was produced by saliva obtained from caries-resistant persons than from caries-susceptible subjects, as determined by incubation with beef broth. Jenkins and co-workers [275] failed to confirm these findings and, in addition, showed that the ammonium ion had no specific inhibitory power on salivary lactate production, the pH of the mixture being the important

268. Dienstein, B.: The Cold War on Dental Caries, J. Am. Dietet. A. **26**:173, 1950. Phillips, P. H.: Relation of Nutrition to Good Teeth, ibid. **26**:85, 1950.

269. Dietary Carbohydrate and Dental Caries, editorial, J. A. M. A. **141**:995 (Dec. 3) 1949.

270. Stearns, G.: The Effectiveness of an Adequate Diet in the Control of Dental Caries, J. Dent. Research **27**:397, 1948.

271. King, J. D.: Dental Caries: Effect of Carbohydrate Supplements on Susceptibility of Infants, Lancet **1**:646, 1948.

272. Cioffari, M. S.: Dietary Control of Dental Caries, Arch. Pediat. **66**:233, 1949.

273. Toverud, G.: Dental Caries in Norwegian Children During and After the Second World War, J. Am. Dietet. A. **26**:673, 1950.

274. Ast, D. B.; Finn, S. B., and McCaffrey, I.: The Newburgh-Kingston Caries Fluorine Study: I. Dental Findings After 3 Years of Water Fluoridation, Am. J. Pub. Health **40**:716, 1950. Schlesinger, E. R.; Overton, D. E., and Chase, H. C.: The Newburgh-Kingston Caries Fluorine Study: II. Pediatric Aspects; Preliminary Report, ibid. **40**:725, 1950.

275. Jenkins, G. N.; Wright, D. E., and Miller, T. K.: Ammonia and Dental Caries, Nature, London **165**:606, 1950.

factor. Granados and associates [276] showed that administration of neither vitamin K nor other quinone derivatives with varying degrees of acid formation-inhibiting power was effective in preventing dental caries in hamsters.

GENERAL STUDIES IN NUTRITION

Stetten [277] has discussed the use of isotopes as metabolic tracers and indicated the types of problem which may be solved with this important tool. The British Medical Association Nutrition Committee [278] has published a comprehensive report of the nutrition situation in Great Britain during and since the war. The report deals with recommended dietary allowances, food consumption studies and clinical and biochemical assessment of the nutritional and health status of the people. In general, food rationing over a period of years has not had a deleterious effect on health, although the diet has been less varied and less palatable. Caloric requirements have been maintained, and supplies of most nutrients have been increased. The recommended dietary allowances of the British Committee differ somewhat from those suggested in this country,[279] the most striking divergence being the lower recommendation for ascorbic acid by the British group. Canada [280] has also published a bulletin outlining the recommended daily intake of specific nutrients for that country. The Canadian suggestions have been developed according to a somewhat different basic concept from that of proposals by the United States or Great Britain, and in general the values are somewhat lower. It is obvious that much more information is needed to determine both minimal and optimal nutrient requirements. A committee of the Food and Agriculture Organization of the United Nations [281] has recently completed an excellent study of caloric requirements which can be used in current planning and as a reference point for further investigation. The dietary needs during prolonged illness have been discussed by McLester.[282]

Several interesting papers have dealt with methods of assessing nutrition, including critical appraisal of those currently in use.[283] Problems encountered in evaluating nutritional status during pregnancy have also been discussed.[284] In several studies various techniques for obtaining information concerning dietary

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276. Granados, H.; Snog-Kjaer, A.; Glavind, J., and Dam, H.: Experimental Dental Caries: XIV. Further Studies on Effect of Certain Quinones, Proc. Soc. Exper. Biol. & Med. **72**:669, 1949.

277. Stetten, D., Jr.: The Use of Isotopes as Metabolic Tracers, Ann. Int. Med. **32**:1, 1950.

278. Report of the Committee on Nutrition, British Medical Association, London, British Medical Association House, 1950.

279. Recommended Dietary Allowances, National Research Council, Food and Nutrition Board, Reprint and Circular Series, No. 129, Washington, October 1948.

280. Canadian Bulletin on Nutrition, Council on Nutrition, Ottawa, March 1950, Vol. 2, No. 1.

281. Calorie Requirements, Committee on Calorie Requirements, United Nations Food and Agricultural Organization, F. A. O. Nutritional Studies No. 5, Washington, D. C., June 1950.

282. McLester, J. S.: Dietary Needs in Long-Term Illness, M. Clin. North America **33**:561, 1949.

283. Sinclair, H. M.: The Assessment of Human Nutriture, in Harris, R. S., and Thiemann, K. V.: Vitamins and Hormones: Advances in Research and Applications, New York, Academic Press, Inc., 1948, Vol. 6, p. 101. Wiehl, D. G.: Statistical Appraisal of Nutritional Data, Federation Proc. **9**:564, 1950. Darby, W. J.: Evaluation of the Symptoms and Signs of Deficiency Diseases, ibid. **9**:592, 1950. Maynard, L. A.: Evaluation of Dietary Survey Methods, ibid. **9**:598, 1950.

284. Scrimshaw, N. S.: Evaluation of Nutrition in Pregnancy, J. Am. Dietet. A. **26**:21, 1950.

intake have been compared.[285] Gilder [286] has reviewed the symptoms and signs of experimentally induced vitamin deficiency in man. In a discussion of the relation of soils to health, Maynard [287] has noted that, with the exception of iodine, no correlations between soil deficiencies in specific areas and human health have been demonstrated.

Trends in food consumption in the United States have been presented by Stiebeling.[288] Dietary studies have been carried out in groups of college students,[289] pregnant women [290] and aging women [291] and the population of a rural area.[292] A series of papers on nutritional status of children has appeared from the research laboratory of the Children's Fund of Michigan.[293] Dietary, medical and biochemical evaluations were carried out, and problems involved in communal feeding were discussed. Signs of malnutrition as observed in several areas of the world, Canada,[294] Nigeria,[295] Madras [296] and Newfoundland,[297] have been reported. Relationships between pregnancy and nutritional status as observed in Newfoundland have also been discussed.[298] Youmans and colleagues [299] studied iron intake and anemia in a rural area of Tennessee. An increase in red cell volume was observed in over one third of the population, and in this group erythrocyte counts were usually below normal. A single injection of folic acid produced slight reticulocytosis in the few subjects so tested.

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285. A Comparison of Technics of Dietary Study, Nutrition Rev. **7**:151, 1949. Some Limitations of Technics for Dietary Study, ibid. **7**:343, 1949.

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Abbott and associates [300] have pointed out that determination of the osseous development of the carpal bones and of the epiphysis of the distal part of the radius and ulna is a valuable procedure in appraisal of nutritional status of school children.

A number of studies on child growth have been conducted and others are in progress.[301] Glaser [302] has studied growth patterns of premature infants. Illingsworth,[303] in a comparison of the weight at birth with weights up to the age of 3 years, has noted a relationship between birth weight and that attained subsequently. Meredith [304] has presented growth data in the form of charts which should be most useful in evaluating the growth record of boys and girls in elementary and high schools. Much more work is needed with various racial groups, under specified conditions, to determine normal rate of growth and the effect of nutrition and other factors on growth. The influence of school lunches [305] and of nutritional education [306] on eating habits of children is under investigation in several parts of the country.

A subject which may become of increasing importance to the medical profession is that of chemicals introduced in the processing of food. Bing [307] has discussed some of the current problems.

Another subject which has aroused much interest and investigation has been that of antivitamins and "toxamins," the latter term having been suggested for substances which interfere with vitamin action for reasons other than chemical analogy.[308] These substances may counteract or increase the need for vitamins, and some antivitamins, such as folic acid antagonists, have been used therapeutically. A review of current knowledge of various antimetabolites has recently been published.[309] An interesting finding in a closely related field has been the demonstration that administration of certain antibiotics stimulates growth in experimental animals.[310] Crystalline aureomycin has been shown to have this activity.[311] Whether this effect is due to an influence on intestinal flora or to some other action remains to be determined.

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Book Reviews

Transactions of Third Conference on Blood Clotting and Allied Problems, 1949. Edited by Joseph E. Flynn. Price, $3. Pp. 231, with 52 charts. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1950.

Those who are familiar with the policy of the Josiah Macy, Jr., Foundation in organizing round table discussions on various clinical phenomena will be pleased to see the "Transactions of the Third Conference on Blood Clotting and Allied Problems." Those who are unfamiliar with the Macy policy may be surprised at the informality of much of the text but cannot fail to be impressed by the unique approach to clinical problems. The opportunity for men from various disciplines to present different aspects of the problem and to ply each other with questions is perhaps not unique in the scientific world, but it reaches a refreshingly informal peak in the Macy Conferences. The "Transactions of the Third Conference on Blood Clotting" includes discussions on a clinical and experimental level of such new anticoagulants as phenylindanedione, ethyl biscoumacetate (tromexan® ethyl acetate) and paritol® (a sulfated mannuronic acid), the first two being somewhat similar to bishydroxycoumarin (dicumarol®) in their action, in that they depress the prothrombin, and the last, paritol,® being considered more as a substitute for heparin. The use of vitamin K in bishydroxycoumarin therapy is discussed in considerable detail, chiefly by members of the Conference who are in the clinical fields. Some of the physiologists, however, contribute materially to this phase of the discussion. Of particular interest is the further elucidation of the physiologic action of bishydroxycoumarin by the use of some of the material labeled with radioactive carbon. The basic concepts of blood coagulation have been of primary interest to this group and the Third Conference devoted a large portion of the two days to the discussion of this field. Zeta potential measurements as a tool for studying certain aspects of blood coagulation; the rate of coagulation of blood and plasma in contact with glass, silicone and similar surfaces; the so-called prothrombin tests; the complexity of the effect of bishydroxycoumarin; the interrelationship of prothrombin, prothrombinogen and labile factor; influence of actual plasma concentration in the final clotting mixture on the response of normal and hemophilic plasmas to thromboplastin; the Iowa two stage analysis of the Quick prothrombin assay using 12.5 per cent saline diluted plasma; the problem of prothrombin determinations in serum, and the two stage plasma prothrombin assay are among the subjects taken up in this volume. The book is necessary to the library of the investigator in the field of blood coagulation, and the clinician who has more than a passing interest in the subject will find it a valuable reference book.

Differential Diagnosis of Internal Diseases. By Julius Bauer, M.D., F.A.C.P. Price, $12. Pp. 866. Grune and Stratton, Inc., 381 4th Ave., New York 16, 1950.

In this book Dr. Bauer makes an attempt to look at the patient as a whole and to discourage the focusing of diagnostic attention on a single set of body systems. He tries to emphasize the need for understanding all the anatomic, physiologic, chemical and psychic disturbances that make the patient sick. The psychogenic factor is particularly stressed. He tries to urge better selection of laboratory tests so that the present tendency to tax both the patient's strength and his pocketbook to obtain a whole battery of data, much of which is noncontributory, can be avoided. There are two main divisions of the book. The first discusses leading signs; the second, leading symptoms. It is abundantly illustrated with cases drawn from the author's own clinical experience. It is a book that will appeal to most internists.

The Pathogenesis and Pathology of Viral Diseases: Symposium Held at New York Academy of Medicine, Dec. 14-15, 1948. Edited by John G. Kidd. Price, $5. Pp. 235, with many illustrations. Columbia University Press, 2960 Broadway, New York 27, 1950.

Here is a small, well printed volume which will be indispensable to teachers and investigators in the field of virology. Most practicing internists will also find it interesting and exciting. For those not actively at work in the field of microbiology, much of the material presented will

be startlingly new. The precision with which most viruses now can be studied and photographed, as illustrated by the excellent reproductions of electron microscope preparations, will be a revelation.

Dr. Richard E. Shope's account of the spread of viruses from infected to susceptible hosts adds another chapter to the brilliant and fascinating story of the elucidation of the epidemiology of infectious disease, ranking possibly in importance with the contributions of Jenner and Pasteur. For instance, in his efforts to determine why epidemics of swine influenza began explosively on many farms in a given area almost simultaneously, he was forced to the conclusion that at least at the start of such epidemics there was operating some other factor than direct spread from one animal to another. By the most painstaking set of investigations it was found, first, that swine influenza was caused by Hemophilus influenzae virus and swine influenza virus working in concert. The reservoir for the virus eventually was found to be the larvae of swine lung worms. These had been parasitized by earthworms which the hogs acquired by rooting in the soil. Three of the developmental stages of the lung worm are spent in the earthworm and the final ones in the hog's body after the earthworm has been ingested. The stimulus which makes the virus thus acquired become activated in the presence of H. influenzae virus is still uncertain, but Shope thinks it is probably meteorological, associated with cold, wet, inclement weather. The possibilities for the elucidation of the spread of human virus diseases opened up by these extremely interesting studies are already challenging numerous capable workers.

In other chapters light is thrown on the relation of cell development and differentiation to susceptibility of the cell to virus invasion and to growth requirements for viruses in the invaded cells. The pathologic changes induced in various types of cells by different viruses are comprehensively described and beautifully illustrated.

The chapters are written by a distinguished group of investigators in microbiology. Together they form a volume which is a worthy successor to the first two volumes resulting from symposia of the section of microbiology of the New York Academy of Medicine, the first being "The Diagnosis of Viral and Rickettsial Diseases," edited by Frank L. Horsfall Jr., and the second "Evaluation of Chemotherapeutic Agents," edited by C. M. MacLeod.

Researches on the Radiotherapy of Oral Cancer. By Constance A. P. Wood and J. W. Boag. No price given. Pp. 148. His Majesty's Stationery Office, 429 Oxford St., London W. 1, 1950.

Carefully controlled experiments were undertaken in the treatment of oral cancers to compare the effects of gamma rays from a radium beam and x-rays of 185 kv. constant potential. The principal difference noted was in the skin reaction. Skin erythema and mucous membrane reaction developed more rapidly and were severer in the patients treated with x-rays. Other experiments demonstrated the ratio of gamma ray dose to x-ray dose for the same severity of skin reaction was 1.34. A new statistical method was developed by the authors for estimating the proportion of patients cured by the use of the interim clinical results. By these methods, the estimated cure rate was 31 per cent for patients treated with radium beam and 19.2 per cent for those treated by x-ray beam. However, the difference of 11.8 per cent is less than 1.62 times its standard error and cannot be considered significant. Serial biopsies were made of 75 lesions (74 patients), and it was found that an accurate prognosis could be made concerning the clinical end result of individual tumors in treated areas. Also, it was found that failure of roentgen therapy may be due to persistence of precancerous lesions in the treated area. The researches conducted are of timely interest and afford a clinical comparison of the effects of differences in wavelength under controlled conditions of treatment. The statistical analyses are provocative and afford methods of estimating the efficacy of therapy without waiting an unduly long period after the completion of the experiment.

Recent Advances in Nutrition with Particular Reference to Protein Metabolism. By Paul R. Canon, Ph.D., M.D., in collaboration with Earl P. Benditt and others. Price, $2. Pp. 74, with 23 charts. University of Kansas Press, Lawrence, Kan., 1950.

The three lectures of which this little volume is composed provide the busy reader with an excellent means of quickly acquainting himself with the newer understanding of the part protein

plays in nutrition. The author and his collaborators have contributed importantly to this field through the development of their so-called rat-repletion method for assessing the nutritive value of individual proteins, protein hydrolysates and amino acid mixtures. The method consists of feeding animals (rats) a protein-deficient, but otherwise adequate, diet until a loss of about 25 per cent of their initial weight has occurred, then feeding the same diet with its protein component replaced by the protein to be evaluated. The latter is added at approximately a 9 per cent level. The resulting repletion is evaluated by a regaining of weight, regeneration of the plasma protein and regeneration of hemoglobin of total carcass protein and of certain antibodies. Amino acids are studied by giving the rats a diet adequate in calories, vitamins and minerals, with a mixture of crystalline amino acids. The removal of any of the nine essential amino acids interrupts repletion. An observation of great practical importance is that all the individual amino acids must be made available to the organism at approximately the same time. It appears that optimal utilization of the amino acids by the tissues is attained only when the indispensable amino acids are presented to the tissues simultaneously. This emphasizes the particular value in nutrition of the high quality proteins in meat, milk, fish and eggs.

Vitamins also receive attention. Several vitamin deficiencies, and particularly lack of riboflavin, lead to a partial block in the process of protein synthesis.

The bearing of this new knowledge on medical treatment in disease and before and after surgical operation is the subject of the concluding lecture. With severe burns and in the course of any of the several wasting diseases, as well as during starvation from whatever cause, the protein of muscle, liver and other organs becomes depleted. Likewise the metabolic activities are reduced, a result presumably of loss of the proteins of which enzymes are composed. Correction of these pathological disturbances involves prevention of further loss of protein and reestablishment of normal processes by giving diets which provide liberal amounts of adequate proteins. In emergencies blood or plasma is injected. It commonly is assumed that the daily needs for protein solely for maintenance approximate 20 to 30 gm. of good quality protein; but in the depleted rat to satisfy requirements for restitution four to five times as much is needed as that required for maintenance, which leads to the supposition that a severely depleted patient should be given not less than five times his minimum maintenance protein requirement.

Dr. Cannon, who is Professor of Pathology at the University of Chicago and a member of the Food and Nutrition Board of the National Research Council, has won wide recognition for his work in immunology and nutrition.

Toxicology of Uranium. Edited by Albert Tannenbaum, M.D. Price, $3. Pp. 333, with charts and tables. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 18, 1951.

This is one of a series of approximately 60 volumes in which is recorded the declassified research work done on the Manhattan Project under the Atomic Energy Commission. It consists of eight chapters dealing with the toxicology of uranium and 16 additional papers of a more or less supplementary nature. It was compiled by 15 authors under the editorship of Dr. Tannenbaum. The papers discuss the absorption, transport, distribution and excretion of uranium, the action of uranium on various enzyme systems, etc., and give a good illustration of the modern technics involved in a survey of the hazards of both acute and chronic exposures to toxic agents.

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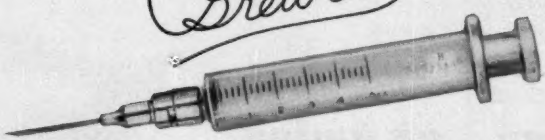

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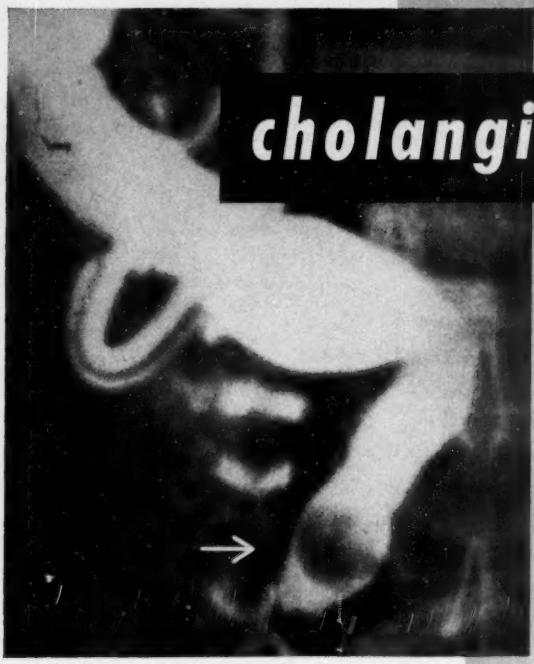

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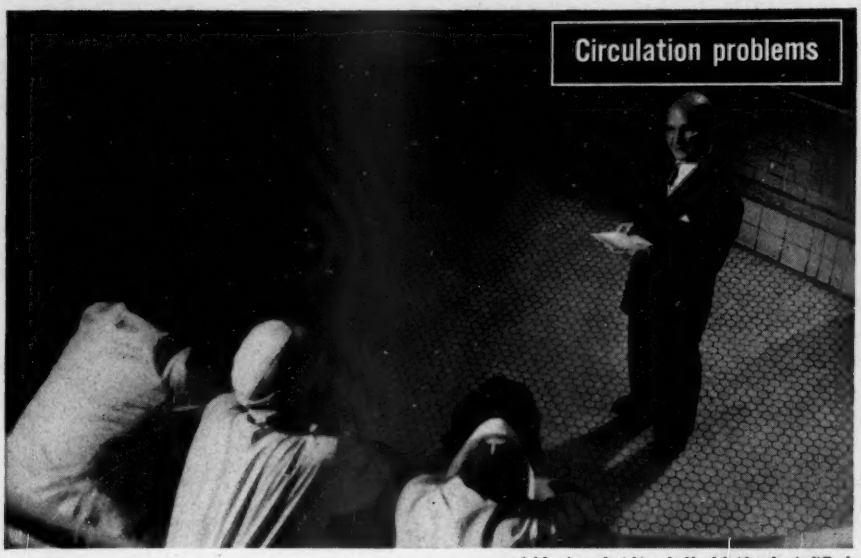

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*Price, P.B., J.A.M.A. *145*:781 (March 17) 1951

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